Acupuncture and Herbal Medicine

Choerospondias axillaris: a review of its clinical application, phytochemistry, and an investigation into its potential cardiovascular therapy

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Abstract

This article conducts a comprehensive review of both traditional therapeutic application knowledge and contemporary literature pertaining to *Choerospondias axillaris* (Roxb.) Burtt et Hill. Traditional application information was gathered from relevant reports, books, and classic material medica. Research literature and dissertations on *C. axillaris* chemical constituents and pharmacological activities, available up to 2023, were sourced from electronic databases. Pharmaceutical components such as flavonoids, phenolic acids, triterpenes, lignans, and organic acids were identified in *C. axillaris* and categorized based on their relevance to cardiovascular roles. Examining the material basis for *C. axillaris* efficacy in addressing cardiovascular diseases, an analysis of 27 Chinese patent medicines containing Choerospondiatis Fructus (CF) highlighted Myristicae Semen as the most frequently utilized and strongly associated with CF in prescriptions. *C. axillaris* exhibited notable pharmacological effects, encompassing anti-myocardial ischemia-reperfusion injury, anti-arrhythmic properties, anti-myocardial fibrosis, and hemorheological effects linked to cardiovascular diseases. This review aspires to provide valuable insights for translating traditional applications into modern pharmaceuticals and offers guidance for clinical applications in cardiovascular interventions.

Keywords: Bioactive components, Cardiovascular diseases, *Choerospondias axillaris*, Traditional therapeutic application

Graphical abstract: https://links.lww.com/AHM/A172.

Introduction

The fruit of *Choerospondias axillaris* (Roxb.) Burtt et Hill (*C. axillaris*) commonly known as "nansuanzao" in China, which is edible and possesses immense economic value. It is primarily distributed in China, Nepal, Japan, India, Thailand, and Vietnam, and has a rich history of utilization in traditional medicine[1]. The dried mature fruit of *C. axillaris* named Choerospondiatis Fructus (CF) in traditional Chinese medicine (TCM) (Figure 1). CF was initially mentioned in the 8th century in the Tibetan medical classic work called "Yuewang Yaozhen," which describes it as having a heart-like appearance and being able to treat heart disease. CF was brought to Mongolia in the latter part of the 13th century. The famous Mongolian medical work "Mongolian Medicine Jinkui" recorded many prescriptions for treating heart disease, most of which contained CF. CF has long played an important role in the clinical application of cardiovascular diseases in Tibetan and Mongol ethnic medicine[2]. Modern research demonstrated that *C. axillaris* fruit extract exhibited significant pharmacological activity of cardiovascular diseases protected including myocardial ischemia-reperfusion injury (MIRI), anti-arrhythmic and anti-myocardial fibrosis, through the pharmacological mechanisms of regulating the inflammatory response, anti-oxidative stress and regulating calcium overload and so on. Furthermore, many other kinds of pharmacological properties including anti-inflammatory effects[3], antidiabetic properties[4], sedative-hypnotic effects[5], kidney stone inhibition[6], immunomodulation[7], hepatoprotection[8], antifatigue[9], antitumour

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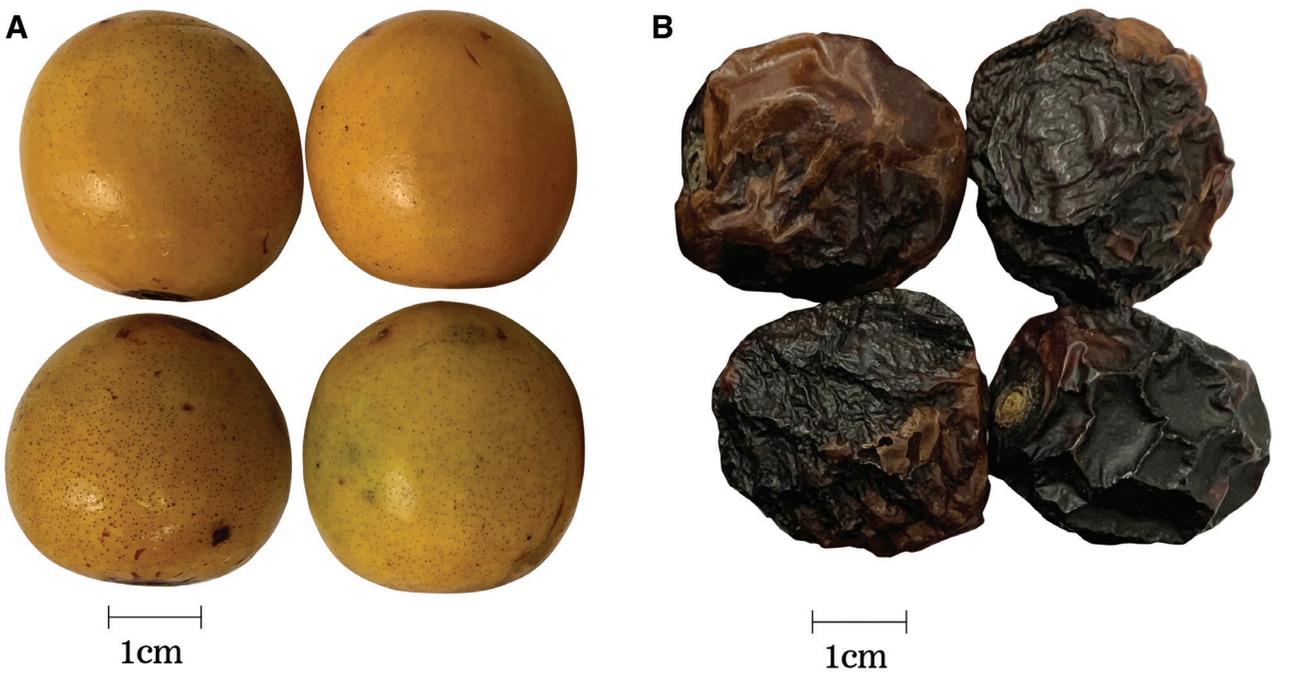


Figure 1. The morphology of *Choerospondias axillaris* fresh fruits (A) and Choerospondias Fructus (B).

activity[10], and antioxidant properties[11–13], revealed more medicinal values of *C. axillaris* fruit.

The remarkable therapeutic effects of *C. axillaris* fruit can be attributed to its complex components. Phytochemical studies have identified various chemical constituents in the plant of *C. axillaris*, including phenolic acids[14], flavonoids[14], lignans[15], coumarins[16], and terpenoids[15], polysaccharides,[17] and volatile constituents[18]. Although dozens of chemical constituents have been isolated and identified from the whole *C. axillaris* plant[19].

The remarkable efficacy of *C. axillaris* fruit in treating cardiovascular diseases in clinical practice has garnered increasing attention from researchers. Recently, only a few reviews have focused on the botanical description, nutritional characteristics, chemical constituents, and pharmacological activities of *C. axillaris*[1–2,20–21], however, this information is insufficient to provide researchers with a comprehensive understanding of *C. axillaris* in both traditional and contemporary research, the main problems were as follow: (1) *C. axillaris* is widely used in TCM for thousands of years and most of the prescription of cardiovascular diseases, but the comprehensive prescription rules of *C. axillaris* in ethnopharmacology is uncleared; (2) the chemical constituents of *C. axillaris* have not been comprehensively reviewed, particularly in the summarizing of polysaccharides and volatile constituents, and the discussion of pharmacodynamic material basis; (3) the lack of systematic exploration in pharmacological mechanisms of cardiovascular protected effects.

Therefore, in the present review, we have comprehensively summarized the traditional therapeutic application, phytochemistry, pharmacological research of cardiovascular protection, and discussed pharmacodynamic material basis, with the objective of enhancing the understanding of the health care knowledge and substantial clinical value of *C. axillaris* in both traditional application and guiding future research endeavors.

Research methodology

The name of *Choerospondias axillaris* (Roxb.) Burtt et Hill was obtained from The Plant List database (https://www.theplantlist.org). Research literature and dissertations related to the chemical constituents and pharmacological activities of *C. axillaris* were retrieved from electronic databases, including the Web of Science, Google Scholar, SciFinder, PubMed, CNKI, Wanfang, and Weipu databases. Keywords used for literature retrieval included *Choerospondias axillaris*, CF, chemical constituents, pharmacological research, clinical applications, and other relevant search terms. Traditional medicine information was collected from the Chinese Pharmacopoeia, relevant published reports and books, and classic material medica. The prescription rules of CF were analyzed by Excel 2021, SPSS Modeller 14.1, and Cytoscape 3.10.0 software. The structures of chemical components were confirmed through literature and SciFinder. The chemical structures were drawn by ChemDraw 19.0. The graphical abstract was created with BioRender.com.

Clinical application

Traditional application

In the clinic of traditional application, CF is a crucial drug for promoting *qi* circulation, blood circulation, nurturing the heart, and calming the mind. Therefore, it is often used as the sovereign drug in prescriptions for the treatment of cardiovascular diseases. The first mention of CF and its potential to heal cardiovascular disease is in Yue Wang Yao Zhen which was written during the 8th century AD in China[21]. The Four

Medical Tantras and Jing Zhu Materia Medica indicated that CF could be employed to improve cardiac pain and restlessness[21]. It was also documented using the Sanwei Tanxiang Powder, which was a prescription and CF was the sovereign drug, for treating cardiovascular diseases[22–24]. In the late 13th century, CF was introduced to Mongolia. It was recorded in Mongolian medical books, such as Mongolian Medicine Jinkui, as a herbal medicine used in alleviating cardiac pain[21]. It also appears as the sovereign drug in Mongolian medicine prescriptions for the treatment of cardiovascular diseases, including Qiwei Guangzao Pills for myocardial ischemia and Roudoukou Wuwei Pills for cardiac pain[25–28]. In the TCM, A Supplement to Compendium of Materia Medica recorded that the fruit of *C. axillari* was edible when it ripened in September. According to Guangxi Chinese herbal medicine, fresh *C. axillari* fruit has the effects of clearing away heat and detoxifying, aiding digestion, and treating burns[29–30].

Modern application

In modern research, the methanol extract of CF can reduce myocardial ischemic injury in rats[31]. A Research institution has also developed a single-ingredient Chinese patent medicine for CF, Xintai Tablets, which can treat coronary heart disease[32] CF is often used in combination with other herbs as a compound prescription in clinical practice. Applying modern scientific and technological means to enhance and improve TCM traditional prescriptions to produce Chinese patent medicines that are convenient for modern clinical use has become an important research topic in the modernization of TCM. At present, there are 27 Chinese patent medicines containing CF for the treatment of cardiovascular-related diseases which have been obtained in the China Pharmacopoeia, Compilation of Chinese Traditional Patent Medicine Standards, Drug Standards of China (Mongolian medicine edition), and Drug Standards of China (Tibetan medicine edition). These Chinese patent medicines are mainly categorized as blood circulation-enhancing and calming formulas, most of the side effects are not yet clear, and gastrointestinal reactions such as nausea and stomach discomfort occasionally[33] (Table 1, sorted from recent to ancient according to publication date and page order). As shown in Table 1, CF is often used as the sovereign drug or minister drug in prescriptions to treat cardiovascular diseases, demonstrating its significance in this regard. Among them, Guangxin Shutong Capsules and Sanwei Tanxiang Tang Powder, which use CF as the sovereign drug. They have been thoroughly researched and are commonly used to treat coronary heart disease and chronic heart failure[22,38–41].

A total of 98 TCMs appeared in the above 27 formulations, and the total frequency of TCMs was 356 times (Table 2). It was worth noting that 18 TCMs from 27 formulations were considered the most frequently used with CF, and these TCMs accounted for 51% of all TCMs that have been used with CF. Among all TCM combined with CF, Myristicae Semen occurred as the predominant herb, which appeared 26 times in 27 formulations. The following was Aquilariae Lignum Resinatum with 23 times, and the next was Aucklandiae Radix with 19 times.

Based on the information of 27 formulations described earlier, the association of all herbs in 27 formulations that contained CF were further analyzed statistically using SPSS Modeller 14.1 and visualized using Cytoscape 3.10.0 software (Figure 2). The core herbs of formulations containing CF were summarized as follows: CF, Myristicae Semen, Aquilariae Lignum Resinatum, Aucklandiae Radix, Caryophylli Flos, Chebulae Fructus, mostly belong to Chinese herbal medicine with a warm nature. Myristicae Semen exhibited the highest frequency of usage and the strongest association with CF. In the famous Tibetan medicine prescription Sanwei Tanxiang Tang Powder, CF is the sovereign drug to promote *qi* and blood circulation, nourish the heart and calm the mind, and Myristicae Semen is the minister drug to enhance the effect of promoting *qi* and blood circulation of the whole prescription to correspond to chest pain caused by blood stasis, which includes coronary heart disease and arrhythmia in modern medicine[42]. Modern research has demonstrated that the combination of CF and Myristicae Semen could reduce the oxidative damage in Wistar rat myocardial cells[43]. Among the formulations from Mongolian and Tibetan ethnic groups, Myristicae Semen was frequently employed in the treatment of cardiovascular diseases[26–27]. Modern research had further evaluated its anti-platelet aggregation properties[44], inhibition of platelet activation[45], and cardioprotective effects[43]. Aquilariae Lignum Resinatum and Aucklandiae Radix are Chinese herb medicines known for their efficacy in promoting *qi* circulation and pain alleviation[46–48]. Together with CF, they can enhance *qi* and relieve pain, relieving symptoms of angina pectoris caused by coronary heart disease. Modern studies have also shown that Aquilariae Lignum Resinatum is effectively used in the treatment of angina pectoris associated with coronary artery disease[49]. Aucklandiae Radix is employed to address abdominal fullness and pain, as well as its potential anti-atherosclerotic effects[50]. According to the principles of TCM theory, it was obvious that the formulations contained CF emphasized a therapeutic approach to dispelling cold, promoting *qi* circulation, and relieving pain. This made them well-suited for treating the conditions of cold stagnation, *qi* stagnation, and blood stasis. Notably, arrhythmia and coronary heart disease are predominant among the conditions treated by formulations containing CF, with primary manifestations such as palpitations, insomnia, chest pain, and restlessness.

Phytochemistry

The previous phytochemical study contributed to the interpretation of the chemical constituents of the fruits, bark, branches, and leaves of *C. axillaris*, revealing 72 constituents, including the major flavonoids, polyphenols, triterpenes, and organic acids. Their structures are shown in Figures 3 and 4, and their names, molecular formulas, molecular weights, extractions, and references are listed in Table 3.

Table 1

Clinical uses of Choerospondias Fructus for the treatment of cardiovascular diseases in China

No.	Chinese patent medicine name	Main compositions	Formulation	Indications	Side effects	Reference
1	Shiwuwei Chenxiang Pills	Aquilariae Lignum Resinatum 100 g; Radix Inulae Racfmosae 150 g; Santali Albi Lignum 50 g; Lignum Pterocarpi Indici 150 g; Carthami Flos 100 g; Myristicae Semen 25 g; Pegaeophyti Radix Et Rhizoma 150 g; Ramulus Rubi 200 g; Caulis Tinosporae 100 g; Zingiberis Rhizoma 50 g; Calciosintiv 100 g; Choerospondias Fructus 50 g; Chebulae Fructus 150 g; Terminaliae Belliricae Fructus 80 g; Phmllanthi Fructus 100 g.	Pill	Chest pain, dry cough, shortness of breath, insomnia	Not yet clear	[34]
2	Shiliuwei Dongqing Pills	Ilicis Chinensis Folium 150 g; Semen Punicae Granati 25 g; Gypsum Fibrosum 75 g; Cinnamomi Cortex 50 g; Amomi Fructus Rotundus 50 g; Aucklandiae Radix 50 g; Caryophylli Flos 50 g; Glycyrrhizae Radix Et Rhizoma 50 g; Fructus Vitis Albus 125 g; Aquilariae Lignum Resinatum 75 g; Bistortae Rhizoma 75 g; Piperis Longi Fructus 50 g; Myristicae Semen 50 g; Carthami Flos 50 g; Choerospondias Fructus 50 g; Eriochir Sinesis Corpus 50 g.	Pill	Chest fullness, abdominal distension, dizziness, edema, cold cough, phlegm asthma due to excessive phlegm	Not yet clear	[34]
3	Qiwei Guangzao Pills	Choerospondias Fructus 450 g; Myristicae Semen 75 g; Caryophylli Flos 75 g; Aucklandiae Radix 75 g; Liquidambaris Resina 75 g; Aquilariae Lignum Resinatum 75 g; Cor Et Haema Bovis Grunnientis 75 g.	Pill	Chest stuffiness and pain, palpitations and shortness of breath, restlessness, insomnia and forgetfulness	Not yet clear	[34]
4	Bawei Chenxiang Powder	Aquilariae Lignum Resinatum 200 g; Myristicae Semen 100 g; Choerospondias Fructus 100 g; Calciosinti 100 g; Olibanum 100 g; Aucklandiae Radix 100 g; Chebulae Fructus 100 g; Gossampini Flos 100 g.	Powder	Coronary heart disease, angina pectoris	Not yet clear	[34]
5	Bawei Qingxin Chenxiang Powder	Aquilariae Lignum Resinatum 180 g; Choerospondias Fructus 180 g; Santali Albi Lignum 90 g; Lignum Pterocarpi Indici 90 g; Carthami Flos 90 g; Myristicae Semen 60 g; Bambusae Concretio Silicea 60 g; Glehniae Radix 60 g.	Powder	Chest stuffiness and pain, palpitations and shortness of breath	Not yet clear	[34]
6	Guangxin Shutong Capsules	Choerospondias Fructus 480 g; Salviae Miltiorrhizae Radix Et Rhizoma 240 g; Caryophylli Flos 60 g; Borneolum 30 g; Bambusae Concretio Silicea 30 g.	Capsule	Coronary heart disease, angina pectoris; chest stuffiness and pain, palpitations and shortness of breath	Gastrointestinal reactions such as nausea and stomach discomfort occasionally	[34]
7	Bawei Sanxiang Powder	Aquilariae Lignum Resinatum 161.3 g; Chebulae Fructus 129 g; Myristicae Semen 129 g; Aucklandiae Radix 129 g; Choerospondias Fructus 193.6 g; Gossampini Flos 96.8 g; Gypsum Fibrosum 96.8 g; Liquidambaris Resina 64.5 g.	Powder	Chest tightness, chest pain, palpitations	Not yet clear	[35]
8	Jiuwei Chenxiang Capsules	Aquilariae Lignum Resinatum 48 g; Myristicae Semen 80 g; Choerospondias Fructus 80 g; Angelicae Sinensis Radix 80 g; Vladimiriae Radix 80 g; Astmgali Radix 144 g; Panacis Quinquefolii Radix 112 g; Chebulae Fructus 48 g; Gossampini Flos 80 g; Amylum 28 g.	Capsule	Coronary heart disease, angina pectoris, cerebral infarction	Not yet clear	[35]

(*Continued*)

Table 1
(Continued)

No.	Chinese patent medicine name	Main compositions	Formulation	Indications	Side effects	Reference
9	Chenxianganshen Capsules	Aquilariae Lignum Resinatum 15 g, Lignum Pterocarpi Indici 10 g; Carthami Flos 10 g; Amomi Fructus Rotundus 10 g; Chebulae Fructus 10 g; Inulae Flos 10 g; Asari Radix Et Rhizoma 10 g; Aconiti Kusnezoffii Radix Cocta 10 g; Gossampini Flos 10 g; Picrorhizae Rhizoma 10 g; Commiphorae Muklis Resina 10 g; Liquidambaris Resina 5 g; *Ramulus syringae* 15 g; Santali Albi Lignum 10 g; Gypsum Fibrosum 10 g; Myristicae Semen 10 g; Tsaoko Fructus 10 g; Gardeniae Fructus 10 g; Pulsatillae Radix 10 g; Dianthi Herba 10 g; Semen Punicae Granati 10 g; Glehniae Radix 10 g; Caryophylli Flos 10 g; Aucklandiae Radix 10 g; Violae Herba 10 g; Sophorae Flavescentis Radix 10 g; Toosendan Fructus 10 g; Ramulus Rubi 10 g; Kaempferiae Rhizome 10 g; Choerospondias Fructus 10 g; Cor Leporis 10 g; Inulae Radix 10 g; Moschus 0.05 g; Dalbergiae Odoriferae Lignum 15 g; Strychni Semen (stir-baked)10 g.	Capsule	Chest distress and asthma, dry cough with little phlegm, stabbing pain, palpitations, insomnia, delirium	Not yet clear	[35]
10	Xiangjuhuoxue Pills	Aquilariae Lignum Resinatum 150 g; Myristicae Semen 100 g; Flos Pyrethri Tatsienense 100 g; Caryophylli Flos 100 g; Choerospondias Fructus 75 g; Liquidambaris Resina 125 g; Aucklandiae Radix 100 g; Kaempferiae Rhizoma 100 g; Margarita100 g; Zotae 25g; Strychni Semen (stir-baked) 25 g.	Pill	Migraine, vascular headache, neuralgia	Not yet clear	[35]
11	Yuzanqingyan shiwuwei Powder/Pills	Flower of Fragrant Plantainlily 90 g; Gypsum Fibrosum 54 g; Gardeniae Fructus 105 g; Glycyrrhizae Radix Et Rhizoma 24 g; Toosendan Fructus 15 g; Glehniae Radix 33 g; Caryophylli Flos 18 g; Aucklandiae Radix 36 g; Choerospondias Fructus 30 g; Chebulae Fructus 36 g; Aquilariae Lignum Resinatum 24 g; Dianthi Herba 39 g; Santali Albi Lignum 15 g; Sophorae Flavescentis Radix 33 g; Myristicae Semen 30 g.	Powder/pill	Swelling and pain in the throat., asthma, hoarse voice, stabbing pain in the chest and rib	Not yet clear	[36]
12	Rongkou Wuwei Pills	Myristicae Semen 100 g; Inulae Radix 80 g; Aucklandiae Radix 80 g; Choerospondias Fructus 50 g; Piperis Longi Fructus 10 g.	Pill	Vexation, insomnia, restlessness	Not yet clear	[36]
13	Anshenzhenjing Ershiwei Pills	Aquilariae Lignum Resinatum 100 g; Myristicae Semen 60 g; Citri Reticulayae Pericarpium Viride 60 g; Choerospondias Fructus 60 g; Aucklandiae Radix 60 g; Gypsum Fibrosum 60 g; Paridis Rhizoma 40 g; Semen Herpetospermi (stir-baked) 40 g; Inulae Flos 40 g; Santali Albi Lignum 40 g; Liquidambaris Resina 40 g; Aconiti Kusnezoffii Radix Cocta 40 g; Commiphorae Muklis Resina 40 g; Strychni Semen (stir-baked) 40 g; Caryophylli Flos 40 g; Cor Susis 40 g; Chrysanthemi Flos 40 g; Polygalae Radix 40 g; Platycodonis Radix 40 g; Susis Fellis 10 g.	Pill	Shortness of breath, restlessness, chest pain	Not yet clear	[36]
14	Chenxianganshen Powder	Aquilariae Lignum Resinatum 30 g, Lignum Pterocarpi Indici 20 g; Carthami Flos 20 g; Amomi Fructus Rotundus 20 g; Chebulae Fructus 20 g; Inulae Flos 20 g; Asari Radix Et Rhizoma 20 g; Aconiti Kusnezoffii Radix Cocta 20 g; Gossampini Flos 20 g; Picrorhizae Rhizoma 20 g; Commiphorae Muklis Resina 20 g; Liquidambaris Resina 10 g; *Ramulus syringae* 30 g; Santali Albi Lignum 20 g; Gypsum Fibrosum 20 g; Myristicae Semen 20 g; Tsaoko Fructus 20 g; Gardeniae Fructus 20 g; Pulsatillae Radix 20 g; Dianthi Herba 20 g; Semen Punicae Granati 20 g; Glehniae Radix 20 g; Caryophylli Flos 20 g; Aucklandiae Radix 20 g; Violae Herba 20 g; Sophorae Flavescentis Radix 20 g; Toosendan Fructus 20 g; Ramulus Rubi 20 g; Kaempferiae Rhizome 20 g; Choerospondias Fructus 20 g.	Powder	Chest distress and asthma, dry cough with little phlegm, stabbing pain, palpitations, insomnia, delirium	Not yet clear	[36]

(*Continued*)

Table 1
(Continued)

No.	Chinese patent medicine name	Main compositions	Formulation	Indications	Side effects	Reference
15	Shunqibuxin Shiyiwei Pills	Aquilariae Lignum Resinatum 50 g; Myristicae Semen 40 g; Choerospondias Fructus 60 g; Liquidambaris Resina 20 g; Aucklandiae Radix 40 g; Chebulae Fructus 50 g; Caryophylli Flos 40 g; Ferulae Resina 50 g; Hominis Placenta 50 g; Gypsum Fibrosum 30 g; Gossampini Flos 30 g.	Pill	stabbing pain in the thoracic rib, mania, slurred speech	Not yet clear	[36]
16	Guangxin Qiwei Tablets	Salviae Miltiorrhizae Radix Et Rhizoma 230.4 g; Santali Albi Lignum 25.6 g; Dalbergiae Odoriferae Lignum 51.2 g; Kaempferiae Rhizoma 38.4 g; Myristicae Semen 76.8 g; Choerospondias Fructus 76.8 g; Hippophae Fructus 76.8 g.	Tablet	Coronary heart disease, restlessness, palpitations, angina pectoris	Not yet clear	[36]
17	Binglang Shisanwei Pills	Arecae Semen 60 g; Aucklandiae Radix 36 g; Piperis Longi Fructus 42 g; Aquilariae Lignum Resinatum 120 g; Myristicae Semen 60 g; Choerospondias Fructus 60 g; Aconiti Kusnezoffii Radix Cocta 60 g; Piperis Fructus 42 g; *Halite Violaceous* 30 g; Caryophylli Flos 48 g; Zingiberis Rhizoma 42 g; Angelicae Sinensis Radix 60 g; Descurainiae Semen 60 g.	Pill	Palpitations, insomnia, stabbing pain	Not yet clear	[36]
18	Ershiwei Roudoukuo Powder/Pills	Myristicae Semen 75 g; Dalbergiae Odoriferae Lignum 80 g; Aquilariae Lignum Resinatum 100 g; Calciosintiv 75 g; Choerospondias Fructus 65 g; Carthami Flos 90 g; Fructus Cari 80 g; Caryophylli Flos 40 g; Bulbus Allii (charred by stir-baked) 35 g; Amomi Fructus Rotundus 35 g; Ferulae Resina 20 g; Tsaoko Fructus 35 g; Chebulae Fructus 200 g; Olibanum 100 g; Terminaliae Belliricae Fructus 80 g; Catechu 70 g; Phmllanthi Fructus 100 g; Radix Et Rhizoma Rhodiolae Kirilowii Seu Bergeniae 60 g; Santali Albi Lignum 50 g; Bovis Calculus 1 g.	Powder/pill	Restlessness, trance, insomnia, dizziness, forgetfulness, tinnitus, palpitations	Not yet clear	[37]
19	Shiyiwei Ganlu Pills	Aquilariae Lignum Resinatum 100 g; Myristicae Semen 40 g; Choerospondias Fructus 70 g; Calciosintiv 100 g; Olibanum 50 g; Aucklandiae Radix 80 g; Chebulae Fructus 200 g; Gossampini Flos 60 g; Calcitum (processed with milk) 200 g; Herba Dracocephali Tangutici 180 g; Radix Inulae Racfmosae 150 g.	Pill	Headache, precordial pain, palpitations, irritability, nausea and vomiting, acid reflux	Not yet clear	[37]
20	Shiyiwei Weiming Powder	Aquilariae Lignum Resinatum 50 g; Myristicae Semen 22.5 g; Choerospondias Fructus 40 g; Bambusae Concretio Silicea 75 g; Olibanum 25 g; Aucklandiae Radix 40 g; Chebulae Fructus 125 g; Gossampini Flos 30 g; Caryophylli Flos 25 g; Cor Et Haema Bovis Grunnientis 50 g; Ferulae Resina 50 g.	Powder	Palpitation, insomnia, dizziness	Not yet clear	[37]
21	Shisanwei Maqianzi Pills	Strychni Semen 50 g, Radix Inulae Racfmosae 30 g; Caulis Tinosporae 30 g; Ramulus Rubi 20 g; Zingiberis Rhizoma 5 g; Chebulae Fructus 30 g; Aquilariae Lignum Resinatum 30 g; Myristicae Semen 10 g; Aucklandiae Radix 10 g; Choerospondias Fructus 10 g; Benzoinum 5 g; Herba Meconopsis 20 g; Rubiae Radix Et Rhizoma 15 g.	Pill	Hypertension, chest and back pain, dyspnea, dizziness, tinnitus, swollen gums	Not yet clear	[37]
22	Bawei Chenxiang Pills	Aquilariae Lignum Resinatum 100 g; Myristicae Semen 100 g; Choerospondias Fructus 100 g; Calciosinti 100 g; Olibanum 50 g; Aucklandiae Radix 175 g; Chebulae Fructus 75 g; Gossampini Flos 50 g.	Pill	Coronary heart disease, angina pectoris	Not yet clear	[37]

(*Continued*)

Table 1
(Continued)

No.	Chinese patent medicine name	Main compositions	Formulation	Indications	Side effects	Reference
23	Sanshiwuwei Chenxiang Pills	Aquilariae Lignum Resinatum 50 g; Cinnamomi Glandulifei Lignum 40 g; Ilicis Rotundae Cortex 30 g; Santali Albi Lignum 35 g; Dalbergiae Odoriferae Lignum 60 g; Bambusae Concretio Silicea 50 g; Carthami Flos 50 g; Caryophylli Flos 20 g; Myristicae Semen 17.5 g; Amomi Fructus Rotundus 15 g; Tsaoko Fructus 15 g; Chebulae Fructus (Cored) 50 g; Terminaliae Belliricae Fructus (Cored) 40 g; Phmllanthi Fructus (Cored) 50 g; Aucklandiae Radix 50 g; Choerospondias Fructus 35 g; Radix Inulae Racfmosae 40 g; Ramulus Rubi 75 g; Caulis Tinosporae 50 g; Kaempferiae Rhizoma 25 g; Gossampini Flos 30 g; Strychni Semen 25 g; Olibanum 25 g; Benzoinum 20 g; Herba Corydalis Impatiens 40 g; Herba Saxifragae Umhellulatae 40 g; Herba Lagotis 40 g; Meconopsis Puniceae Herba Et Flos 50 g; Flos Pyrethri Tatsienense 50 g; Cremanthodium Humile Maxim 75 g; Radix Solms-Laubachiae 75 g; Semen Punicae Granati 50 g; Aconiti Penduli Radix 30 g; Cor Et Haema Bovis Grunnientis 15 g; Moschus 0.5 g.	Pill	Cough, reversed flow of qi, arthralgia, cardiopathy	Not yet clear	[37]
24	Sanwei Tanxiang Tang Powder	Santali Albi Lignum 100 g; Myristicae Semen 100 g; Choerospondias Fructus 100 g.	Powder	Clearing away the heat of the heart	Not yet clear	[37]
25	Zhongze Bawei Chenxiang Powder	Aquilariae Lignum Resinatum 50 g; Myristicae Semen 20 g; Caryophylli Flos 20 g; Choerospondias Fructus 40 g; Aucklandiae Radix 42.5 g; Flos Pyrethri Tatsienense 75 g; Cor Leporis30 g; Hominis Placenta 50 g.	Powder	precordial pain, delirium, restlessness	Not yet clear	[37]
26	Anshen Pills	Arecae Semen 50 g; Aquilariae Lignum Resinatum 40 g; Caryophylli Flos 15 g; Myristicae Semen 12.5 g; Aucklandiae Radix 25 g; Choerospondias Fructus 20 g; Kaempferiae Rhizoma 20 g; Piperis Longi Fructus 15 g; Piperis Fructus 17.5 g; *Halite Violaceous* 7.5 g; Aconiti Penduli Radix 15 g; Cor Leporis 7.5 g; Cor Et Haema Bovis Grunnientis 7.5 g; Ferulae Resina 5 g; Saccharum Officinarum Extract 25 g.	Pill	Neurosis, delirium, tinnitus, palpitations	Not yet clear	[37]
27	Changsong Bawei Chenxiang Powder	Aquilariae Lignum Resinatum 50 g; Choerospondias Fructus 20 g; Santali Albi Lignum 20 g, Dalbergiae Odoriferae Lignum 30 g; Myristicae Semen 10 g; Bambusae Concretio Silicea 20 g; Carthami Flos 20 g; Radix Solms-Laubachiae 20 g.	Powder	Chest distress and shortness of breath, chest and back pain, hypertension, cardiovascular disease	Not yet clear	[37]

Flavonoids

Flavonoids are important secondary metabolites with significant antioxidant, antibacterial, cardiovascular protection, and antitumor activities[63]. Twenty-one flavonoids (**1–21**) were reported, mainly isolated from the fruits, leaves, and bark of *C. axillaris*, among which dihydroflavonol (**1–3**), dihydroflavone (**4–8**), flavonoid (**9**), flavonol (**10–14**), and flavanols (**15–21**) are the major flavonoid structure classes in *C. axillaris*.

Five flavonoids (**1**, **10–11**, **13**, and **15**) were isolated from *C. axillaris* fruits. Eleven flavonoids (**2–3**, **6–8**, **12**, **14**, and **18–21**) were described in *C. axillaris* leaves, and five (**4–5**, **9**, and **16–17**) were isolated from bark.

Otherwise, the liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-Q-TOF-MS/MS) method was used to discover more flavonoids in *C. axillaris*. Yang et al.[63] applied HPLC-Q-TOF-MS/MS to analyze the ethanol extract of *C. axillaris* pulp, and six flavonoids were identified from mass data. Among them, quercetin 3-*O*-arabinosyl-glucoside and quercetin 3'-*O*-rhamnoside were first found in *C. axillaris* pulp[63]. The UPLC-Q-TOF-MS/MS analysis revealed 16 procyanidins in the *C. axillaris* pericarp. Type B proanthocyanidin dimer, type B proanthocyanidin trimer, and catechin and catechin gallate polymer were the main proanthocyanidins in *C. axillaris*[64].

The content of total flavonoids in *C. axillaris* fruits was 0.2% to 0.6%, and it was 5.96% in *C. axillaris* leaves, indicating that flavonoids were mainly located in the leaves of *C. axillaris*[65–67]. The quantitative analysis showed that the contents of catechins, vitexin,

Table 2

Frequency of traditional Chinese medicine used in formulations containing Choerospondias Fructus

Traditional Chinese medicine name	Frequency	Percentage (%)
Myristicae Semen	26	7.30
Aquilariae Lignum Resinatum	23	6.46
Aucklandiae Radix	19	5.34
Caryophylli Flos	15	4.21
Chebulae Fructus	14	3.93
Santali Albi Lignum	11	3.09
Gossampini Flos	10	2.81
Carthami Flos	8	2.25
Gypsum Fibrosum	7	1.97
Liquidambaris Resina	7	1.97
Kaempferiae Rhizoma	6	1.69
Olibanum	6	1.69
Amomi Fructus Rotundus	5	1.40
Bambusae Concretio Silicea	5	1.40
Calciosinti	5	1.40
Dalbergiae Odoriferae Lignum	5	1.40
Ramulus Rubi	5	1.40
Strychni Semen	5	1.40

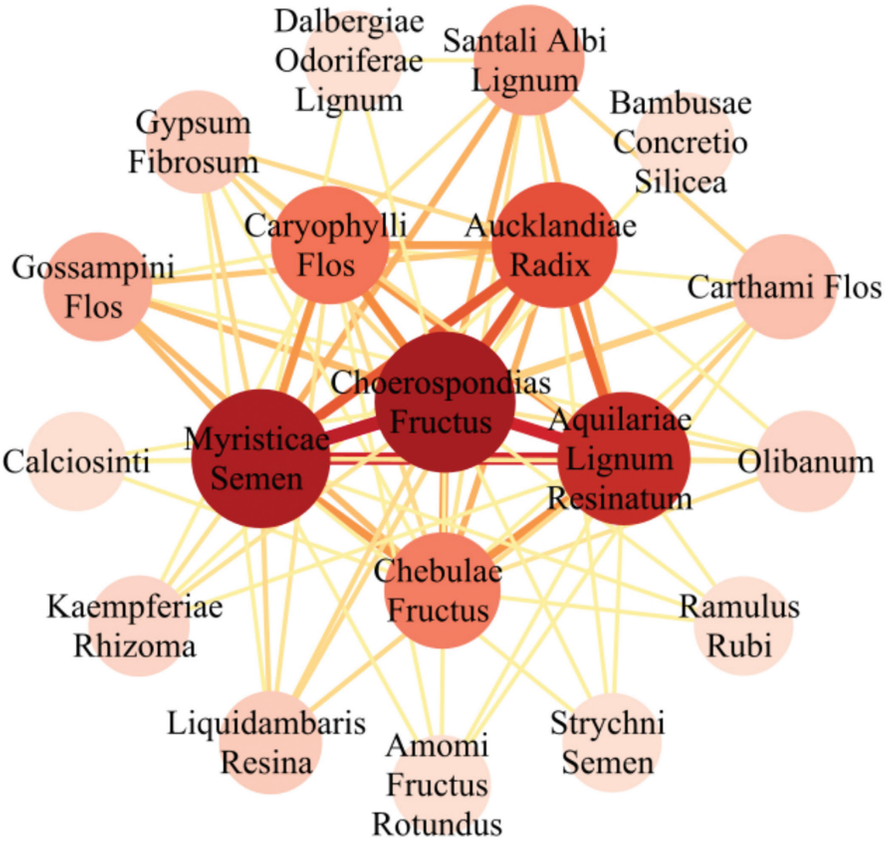


Figure 2. Drug network of Chinese patent medicines containing Choerospondias Fructus for the treatment of cardiovascular diseases.

isoquercitrin, quercetin, astragalin, and isorhamnetin were 117, 12, 45, 484, 60 μm/g, respectively, in *C. axillaris*[68].

Modern pharmacological studies have reported that some constituents within these flavonoids exhibit significant cardiovascular protection effects. Dihydroquercetin

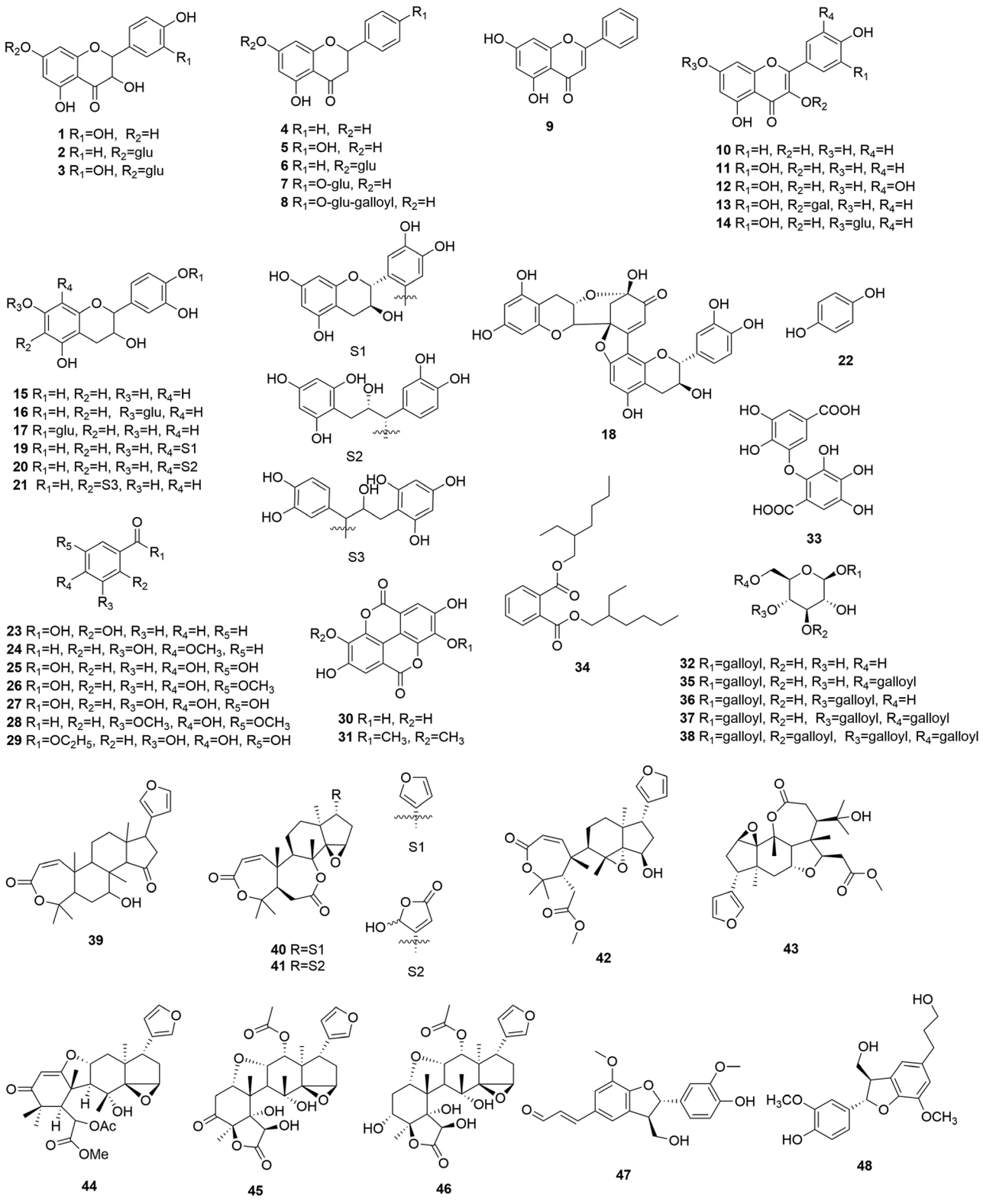


Figure 3. Chemical structure of *Choerospondias axillaris* (1–48).

showed cardiovascular protective effect on H9c2 cells, isolated rat hearts Langendorff perfusion, and human healthy volunteers, through lowering total cholesterol level, inhibiting the apoptotic pathway, and phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway, etc[69–70]. Pinocembrin exhibited significant cardiovascular effects on atrial fibrillation[71], troughing inhibited the reactive oxygen species (ROS)/transforming growth factor-β1 (TGF-β1) pro-fibrotic pathway and the ROS/p-p38 mitogen-activated protein kinase (MAPK) pro-apoptotic pathway. What's more, pinocembrin could ameliorate heart failure, the myocardial infarction of rats which was carried by left anterior descending artery ligation, through nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway[72]. Naringenin has been found in many plants, it is

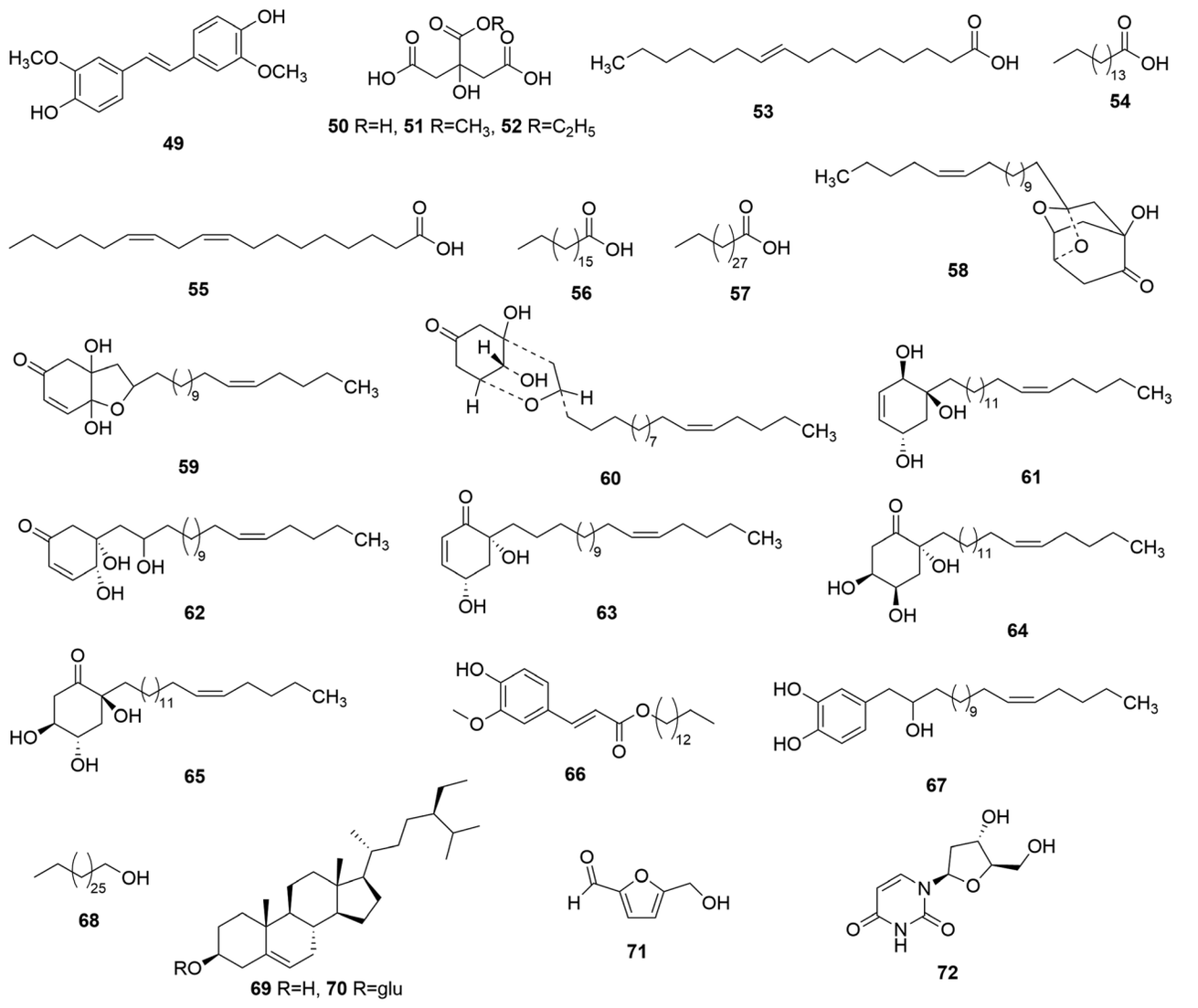


Figure 4. Chemical structure of *Choerospondias axillaris* (49–72).

an important phytochemical in various disorders such as cardiovascular disease, including atherosclerosis and coronary artery disease[73–74], hypertension and cardiac hypertrophy[75], myocardial infarction and ischemic stroke[76–77], and diabetic hearts[78]. Chrysin could be against oxidative and inflammatory to present its cardiovascular protective effect[79]. In the rat model of cardiovascular abnormalities induced by nitric oxide (NO) revealing, kaempferol could cardiovascular malfunction by suppressing the tumor necrosis factor-α (TNF-α) pathway[80]. Quercetin is a common constituent in various plants, it has been proven to benefit hypertension, diabetes, inflammation, and vascular diseases, which relate to cardiovascular diseases[81]. Myricetin exhibits protective roles for cardiovascular diseases, including cardioprotective, anti-atherosclerotic, anti-hypertensive, and anti-hyperlipidemic[82]. Hyperin exhibits the ability to ameliorate electrocardiogram abnormalities, enhance cardiac function, diminish the size of myocardial infarction, and markedly decrease both myocardial fibrosis and oxidation levels[83]. Recent evidence demonstrates that catechins in cardiovascular health are pivotal, operating through mechanisms that encompass reducing blood pressure, enhancing flow-mediated vasodilation, and mitigating atherosclerosis[84].

Phenolics

Phenolics are a group of naturally occurring chemical compounds that contain at least one aromatic nucleus and one or more -OH groups, which are categorized as flavonoids and nonflavonoids[85]. A total of 17 nonflavonoid polyphenols and phenolic acids were isolated from *C. axillaris*, including one phenolic (**22**) and 16 phenolic acids (**23–38**). Among them, night constituents (**22–23**, **25–28**, **30–31**, **34**) were isolated from *C. axillaris* fruits, and six constituents (**29**, **32**, **35–38**) were isolated from *C. axillaris* bark, and two constituents (**24**, **33**) were obtained from *C. axillaris* kernels.

In addition, qualitative analysis using UPLC-Q-TOF-MS/MS revealed new phenolics and phenolic acids from *C. axillaris* pericarp. Jiang et al.[64] reported that chebulic acid, comenic acid, protocatechualdehyde, 3-hydroxybenzoic acid, galloyl ethyl ester, methylellagic acid glucoside, and dimethylellagic acid glucoside, methylellagic acid were first found in *C. axillaris*, but they were not actually isolated and terminally identified.

Table 3

Chemical constituents from *Choerospondias axillaris*

No.	Compound class and name	Molecular formula	Molecular weight	Extraction part	Reference
	Flavonoids				
1	Dihydroquercetin	$C_{15}H_{12}O_7$	304.0583	Fruit	[51]
2	Sinensin	$C_{21}H_{22}O_{11}$	450.1162	Leaf	[52]
3	Taxifolin 7-*O*-β-D-glucoside	$C_{21}H_{22}O_{12}$	466.1111	Leaf	[52]
4	Pinocembrin	$C_{15}H_{12}O_4$	256.0736	Bark	[53]
5	Naringenin	$C_{15}H_{12}O_5$	272.0685	Bark	[53]
6	Pinocembrin-7-*O*-β-D-glucopyranoside	$C_{21}H_{22}O_9$	418.1264	Leaf	[52]
7	Choerospondin	$C_{21}H_{22}O_{10}$	434.1213	Leaf	[52]
8	Narigenin-4′-*O*-(6″-*O*-galloyl-β-D-glucopyranoside)	$C_{28}H_{26}O_{14}$	586.1323	Leaf	[52]
9	Chrysin	$C_{15}H_{10}O_4$	254.0579	Bark	[53]
10	Kaempferol	$C_{15}H_{10}O_6$	286.0477	Fruit	[14,54]
11	Quercetin	$C_{15}H_{10}O_7$	302.0427	Fruit	[14,51,54–55]
12	Myricetin	$C_{15}H_{10}O_8$	318.0376	Leaf	[56]
13	Hyperin	$C_{21}H_{20}O_{12}$	464.0955	Fruit	[14]
14	Quercetin 7-*O*-glucoside	$C_{21}H_{20}O_{12}$	464.0955	Leaf	[52]
15	Catechin	$C_{15}H_{14}O_6$	290.0790	Fruit	[14]
16	Catechin 7-*O*-β-D-glucopyranoside	$C_{21}H_{24}O_{11}$	422.1213	Bark	[57]
17	Catechin 4'-*O*-β-D-glucopyranoside	$C_{21}H_{24}O_{11}$	452.1319	Bark	[57]
18	Dehydrodicatechin A	$C_{30}H_{24}O_{12}$	576.1268	Leaf	[52]
19	Catechol-catechol-6′,8-dimer	$C_{30}H_{26}O_{12}$	578.1424	Leaf	[52]
20	Gambiriin A1	$C_{30}H_{28}O_{12}$	580.1581	Leaf	[52]
21	Gambiriin A3	$C_{30}H_{28}O_{12}$	580.1581	Leaf	[52]
	Phenolic acids				
22	Hydroquinone	$C_6H_6O_2$	110.0368	Fruit	[58]
23	Salicylic acid	$C_7H_6O_3$	138.0317	Fruit	[14,51]
24	Isovanillin	$C_8H_8O_3$	152.0473	Kernel	[15]
25	Protocatechuic acid	$C_7H_6O_4$	154.0266	Fruit	[14,51,54–55,58]
26	Vanillic acid	$C_8H_8O_4$	168.0423	Fruit	[54–55]
27	Gallic acid	$C_7H_6O_5$	170.0215	Fruit	[14,51,54–55,58]
28	Syringaldehyde	$C_9H_{10}O_4$	182.0579	Fruit	[55]
29	Ethyl gallate	$C_9H_{10}O_5$	198.0528	Bark	[59]
30	Ellagic acid	$C_{14}H_6O_8$	302.0063	Fruit	[55,58]
31	3,3′-Di-*O*-methylellagic acid	$C_{16}H_{10}O_8$	330.0376	Fruit	[51,55]
32	1-*O*-Galloyl-β-D-glucose	$C_{13}H_{16}O_{10}$	332.0743	Bark	[59]
33	Dehydrodidallic	$C_{14}H_{10}O_{10}$	338.0274	Kernel	[15]
34	Dioctyl phthalate	$C_{24}H_{38}O_4$	390.2770	Fruit	[14]
35	1,6-Di-*O*-galloyl-β-D-glucose	$C_{20}H_{20}O_{14}$	484.0853	Bark	[59]
36	1,4-Di-*O*-galloyl-β-D-glucose	$C_{20}H_{20}O_{14}$	484.0853	Bark	[59]
37	1,4,6-Tri-*O*-galloyl-β-D-glucose	$C_{27}H_{24}O_{18}$	636.0963	Bark	[59]
38	1,3,4, 6-Tetra-*O*-galloyl-β-D-glucose	$C_{34}H_{28}O_{22}$	788.1072	Bark	[59]
	Triterpenes				
39	Ouabanginone	$C_{26}H_{34}O_5$	426.2406	Branches and leaves	[16]

(*Continued*)

Table 3
(Continued)

No.	Compound class and name	Molecular formula	Molecular weight	Extraction part	Reference
40	Surenolactone	$C_{26}H_{32}O_6$	440.2199	Branches and leaves	[16]
41	Axillariol A	$C_{26}H_{32}O_8$	472.2097	Branches and leaves	[16]
42	Toonaciliatins H	$C_{27}H_{36}O_7$	472.2461	Branches and leaves	[16]
43	Toonaciliatins D	$C_{27}H_{36}O_8$	488.2410	Branches and leaves	[16]
44	Toonayunnanin I	$C_{29}H_{36}O_9$	528.2359	Branches and leaves	[16]
45	Toonaciliatins N	$C_{27}H_{32}O_{11}$	532.1945	Branches and leaves	[16]
46	Toonaciliatins O	$C_{27}H_{34}O_{11}$	534.2101	Branches and leaves	[16]
	Lignans				
47	Balanophonin	$C_{20}H_{20}O_6$	356.1260	Kernel	[15]
48	(-)-(7*R*, 8*S*)-Dihydrodehydrodiconifenyl alcohol	$C_{20}H_{24}O_6$	360.1573	Kernel	[15]
	Others				
49	(*E*)-3,3'-Dimethoxy-4,4'-dihydroxystilbene	$C_{16}H_{16}O_4$	272.1049	Kernel	[15]
50	Citric acid	$C_6H_8O_7$	192.0270	Fruit	[14,55,58]
51	2-Hydroxy-1, 2, 3-propane tricarboxylic acid-2-methyl ester	$C_7H_{10}O_7$	206.0427	Fruit	[14]
52	2-Hydroxy-1, 2, 3-propane tricarboxylic acid-2-ethylester	$C_8H_{12}O_7$	220.0583	Fruit	[14]
53	Palmitoleic acid	$C_{16}H_{30}O_2$	254.2246	Kernel	[15]
54	Palmitic acid	$C_{16}H_{32}O_2$	256.2402	Fruit	[14]
55	Linoleic acid	$C_{18}H_{32}O_2$	280.2402	Fruit	[60]
56	Stearic acid	$C_{18}H_{36}O_2$	284.2175	Fruit	[14]
57	Triacontanoic acid	$C_{30}H_{60}O_2$	452.4593	Fruit	[51]
58	(1*S*, 3*R*, 5*R*, 8*R*)-5-Hydroxy-3-(*Z*-heptadec-12-enyl)-2,10-dioxa-tricyclo[3.2.2.1^{3,8}]decan-6-one	$C_{25}H_{42}O_4$	406.3083	Fruit	[61]
59	3a, 7a-Dihydroxy-2-(*Z*-heptadec-12-enyl)-2,3,3a,4-tetrahydro-(7a H)-benzofuran-5-one	$C_{25}H_{42}O_4$	406.3083	Fruit	[61]
60	(1*R*, 3*S*, 5*R*, 9*S*)-5,9-Dihydroxy-3-(*Z*-heptadec-12-enyl)-2-oxa-bicyclo[3.3.1]nanan-7-one	$C_{25}H_{44}O_4$	408.3240	Fruit	[61]
61	2-(*Z*-Nonadec-14-enyl)-cyclohex-5-ene-1,2,4-triol	$C_{25}H_{46}O_3$	394.3447	Fruit	[61]
62	4,5-Dihydroxy-5-(*Z*-2-hydroxyl-nonadec-14-enyl)-cyclohex-2-enone	$C_{25}H_{44}O_4$	408.3240	Fruit	[61]
63	4,6-Dihydroxy-6-(*Z*-nonadec-14-enyl)-cyclohex-2-enone	$C_{25}H_{44}O_3$	392.3290	Fruit	[61]
64	(2*R*, 4*R*, 5*S*)-2,4,5-Trihydroxy-2-(*Z*-nonadec-14-enyl)-cyclohexanone	$C_{25}H_{46}O_4$	410.3396	Fruit	[61]
65	(2*S*, 4*S*, 5*S*)-2,4,5-Trihydroxy-2-(*Z*-nonadec-14-enyl)-cyclohexanone	$C_{25}H_{46}O_4$	410.3396	Fruit	[61]
66	Tetradecyl E-ferulate	$C_{24}H_{38}O_4$	390.2770	Bark	[53]
67	4-(*Z*-2-Hydroxynonadec-14-enyl)-benzene-1,2-diol	$C_{25}H_{42}O_3$	390.3134	Fruit	[61]
68	Octacosanol	$C_{28}H_{58}O$	410.4488	Fruit	[51]
69	β-Sitosterol	$C_{29}H_{50}O$	414.3862	Fruit	[14,51,54]

(*Continued*)

Table 3
(Continued)

No.	Compound class and name	Molecular formula	Molecular weight	Extraction part	Reference
70	Daucosterol	$C_{35}H_{60}O_6$	576.4390	Fruit	[14,51]
71	5-Hydroxymethylfurfural	$C_6H_6O_3$	126.0317	Kernel	[15]
72	5-Methyl-3', 5'-di-*O*-(p-chlorobenzoyl)-2'-deoxyuridine (deoxyuridine)	$C_9H_{12}N_2O_5$	228.0746	Fruit	[62]

The total phenolics content in the *C. axillaris* fruit extract was 56.8% (w/w) of the extracted material[66], and approximately 62% in *C. axillaris* fruit peel[11]. Quantitative analysis was used to evaluate the content of phenolic acids in *C. axillaris*. Liquid chromatography-triple quadrupole-quadrupole-mass spectrometry (LC-QQQ-MS/MS) analysis showed that protocatechuic acid (18 mg/g) gallic acid (1.3 mg/g) and ellagic acid (0.8 mg/g) were abundant phenolic constituents in the total flavonoid extract of *C. axillaris*[68].

Phenolic acids are significant constituents in *C. axillaris*. Protocatechuic acid can attenuate isoproterenol-induced cardiac hypertrophy in mouse model by downregulation of ROCK1-Sp1-PKCγ axis[86], and protect cardiomyocytes in doxorubicin- and arsenic trioxide-induced toxicity[87]. Vanillic acid exhibited the capability to suppress the activation of various genes, including adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), NOD-like receptor family pyrin domain-containing protein (NLRP), nuclear factor-kappa B (NF-κB), signal transducer and activator of transcription (STAT), toll-like receptor (TLR), mechanistic target of rapamycin (mTOR), MAPK, cyclooxygenase (COX)-2, and inducible nitric oxide synthase (iNOS), which are implicated in inflammatory response and oxidative stress pathways, thereby influencing the onset and progression of cardiovascular diseases[88]. Gallic acid exhibits protective effects against cardiovascular diseases by enhancing the capacity of antioxidant enzymes, inhibiting lipid peroxidation, and lowering serum levels of cardiac marker enzymes. Additionally, it modulates hemodynamic parameters, facilitates the recovery of electrocardiogram abnormalities, and preserves histopathological structures, thereby contributing to its cardioprotective effect[89]. Ellagic acid could potentially offer therapeutic benefits for cardiovascular diseases, it may regulate lipid metabolism imbalance, production of pro-inflammatory factors, proliferation of vascular smooth muscle cells, apoptosis of cardiomyocytes, endothelial cell dysfunction, as well as the intake and release of Ca^{2+}[90].

Triterpenes

Triterpenes are a group of naturally occurring chemical constituents whose structure includes 30 elements of carbon, and they are composed of isoprene units[91]. Limonoids are highly oxygenated triterpenes, with the side chain cyclized into a furan ring but they have lost the terminal 4 carbon atoms of the side chain[92]. Eight limonoids (**39–46**) were isolated from *C. axillaris* branches and leaves.

Additionally, two lignans (**47–48**) were isolated from *C. axillaris* kernels. Twenty-four other type constituents were isolated from *C. axillaris*, including one stilbene (**49**), three organic acids (**50–52**), five fatty acids (**53–57**), one tricyclic ketone (**58**), two dicyclones (**59–60**), two cyclohexenes (**61–62**), three cyclohexanones (**63-65**), two aromatic long-chain fatty acids (**66–67**), one fatty alcohol (**68**), two sterols (**69–70**), and two other types of constituents (**71–72**).

Polysaccharides

Polysaccharides are a group of biological macromolecules composed of more than 10 simple sugars that are sequentially connected through glycosidic bonds. Plant polysaccharides are abundantly available and have no toxic side effects, which makes them possess a diverse range of functional properties and biological activities[93]. In recent years, water extraction, alkaline extraction, ultrasonic-assisted extraction, and enzyme-assisted extraction have been used to study the polysaccharide extraction rate. The results showed that enzyme-assisted extraction was the most efficient extraction method, and the polysaccharide yield reached 17.3%[94]. Four purified polysaccharide fractions were isolated from *C. axillaris*. Among them, two polysaccharides (ultrasound-assisted extracted polysaccharides [UP] and polysaccharides extracted by hot water [HP]) were isolated from fruit peels, and two (*choerospondias axillaris* leaf polysaccharides [CALP]-1 and CALP-2) were obtained from leaves (Table 4). However, the structural features of these four polysaccharides have not been elucidated.

Volatile constituents

A total of 78 volatile constituents were identified from *C. axillaris* by gas chromatography-mass spectrometry (GC-MS) analysis (Table 5), including 11 alcohols (**V1–V11**), 12 aldehyde ketones (**V12–V23**), four alkenes (**V24–V27**), 28 aromatics (**V28–V55**), eight esters (**V56–V63**), four organic acids (**V64–V67**), and 11 other types of volatile constituents (**V68–V78**). Fifty-nine compounds (**V4–V11**, **V16–V23**, **V26–V27**, **V37–V55**, **V57–V58**) were determined from *C. axillaris* fruits, and 19 other compounds (**V1–V3**, **V12–V15**, **V24–V25**, **V28–V36**, **V56**) were determined from *C. axillaris* wood. The major compounds of *C. axillaris* fruits were hydroxyacetic acid (7.46%), 2(5H)-furanone (6.26%), carbamicacid-monoammoniumsalt(5.65%),2-methoxy-4-vinylphenol (5.14%), ammonium acetate (4.02%), propanoic acid, 2-oxo-methyl ester (3.14%), and 1-hydroxy-2-propanone (2.94%)[18,95].

Table 4

Structural characteristics of the purified polysaccharides from *Choerospondias axillaris*

Polysaccharide fraction	Extraction, separation, and purification procedure	M_w (kDa)	Monosaccharide composition	Structural feature	Extraction part	Reference
UP	Ultrasound-assisted extraction (50℃), dialysis bag	127.7	Ara (67.1%), Gal (33.8), Glc (21.7%), Man (8.9%), Rha (4.1), Xyl (2.3%)	/	Fruit peels	[17]
HP	Hot water extraction (90℃), dialysis bag	225.6	Glc (77.8%), Ara (46.2%), Gal (24.7%), Rha (3.2%), Man (2.5%)	/	Fruit peels	[17]
CALP-1	Hot water, DEAE-52 cellulose ion exchange column, Sephadex G-100 column	11.2	Glc (27.18%), Gal (5.50%), Rha (5.16%), Ara (2.31%), Galacturonic acid (1.07%), Xyl (1.00%), Man (0.76%), Glucuronic acid (0.22%)	/	Leaves	[13]
CALP-2	Hot water, DEAE-52 cellulose ion exchange column, Sephadex G-100 column	8.03	Gal (18.84%), Glc (8.28%), Ara (3.63%), Galacturonic acid (1.45%), Rha (1.38%), Glucuronic acid (0.07%)	/	Leaves	[13]

CALP: *Choerospondias axillaris* leaf polysaccharides; DEAE: Diethylaminoethyl; HP: Polysaccharides extracted by hot water; UP: Ultrasound-assisted extracted polysaccharides.

Cardiovascular therapeutic activities

C. axillaris has traditionally been used for the treatment of cardiovascular diseases, and it is used in Mongolian and Tibetan medicine for heart angina and palpitations[2]. This therapeutic action may be attributed to its main components including flavonoids[14], phenolics[14], lignans[15], and organic acids[55] from *C. axillaris*. In recent years, preclinical studies of *C. axillaris* revealed that anti-MIRI, anti-arrhythmic, and anti-myocardial fibrosis were the main pharmacological effects which were relevant to cardiovascular diseases. Recent researches have tried hard to elucidate the cardiovascular protection and mechanisms of *C. axillaris*, with a focus on myocardial ischemia (Figure 5). Furthermore, the other main pharmacological effects associated with cardiovascular therapeutic activities, such as antioxidant and anti-inflammatory effects were conducted in many studies. Therefore, the cardiovascular therapeutic activities of *C. axillaris* were comprehensively summarized in the present review (Table 6).

Anti-MIRI

MIRI is a significant complication in the clinical treatment of myocardial infarction. In the process of reperfusion, oxidative stress in myocardial cells is generated under the adverse condition of increasing xanthine oxidase production, the respiratory burst of neutrophil, metabolism, and dysfunction of mitochondrial electron transport chain[113]. Then, the increase in ROS causes a decrease in membrane fluidity and an increase in calcium ion permeability, these changes lead to the more severe cellular calcium overload and mitochondrial damage[114]. Meanwhile, these changes also result in the alteration of cell membrane proteins and increase the level of cardiac troponin I (cTnI) and creatine kinase-MB (CK-MB)[115–116]. Finally, after a series of changes, the progress of autophagy, apoptosis, programmed death, and necrosis developed in cells, then lead to myocardial injury, myocardial dysfunction, arrhythmias, and microvascular blockage[117–118].

Previous studies have shown that the total flavonoids of CF (TFC) or total flavonoids of CF leaf (TFCL) significantly improved the bradycardic effect caused by the experimental rats resisting pituitary hormones, and shorten the time of heart rate recovery[96], reduced the occurrence of ventricular tachycardia (VT), shorten the duration of ventricular fibrillation (VF), regulated the protein expression profile of myocardial tissue, and attenuated serum CK activity, decreased TNF-α, interleukin-6 (IL-6), and malonaldehyde (MDA) levels, and increased NO and interleukin-10 (IL-10) levels[100–101].

ROS is an important factor that promotes cellular damage during MIRI. The anti-oxidative stress effect of TFC in MIRI took effect by reducing the content of MDA and increasing the levels of catalase (CAT), glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) in heart tissue homogenates[97]. Additionally, TFC significantly decreased the cell death promoter Bax, increased the expression of the apoptosis repressor B-cell lymphoma-2 (Bcl-2), cell apoptosis factor caspase-3, and downregulated activation of p38 MAPK and c-jun N-terminal kinase (JNK), indicating that the treatment of myocardial ischemia by CF was mediated by the MAPK signaling pathway[97]. NF-κB can be activated after MIRI[119], and further promotes inflammation and fibrosis in the progression of ventricular remodeling. This condition can be improved by suppression of the NF-κB signaling pathway[120]. TFC could regulate inflammatory cytokines, inhibit matrix metalloproteinases (MMPs) levels and TGF-β1 and phosphorylation inhibitory subunit of NF-κBα (p-IKBα) expression, and block the NF-κB signaling pathway to exert cardioprotective effects[98]. Moreover, ethanol extracts of CF significantly improved the electrocardiogram in MIRI rats, decreased the myocardial infarct size, and alleviated the degree of myocardial ischemic injury[31]. Total organic acids of CF significantly reduced the myocardial infarct area and improved the quality of infarcted areas in rats undergoing ischemia-reperfusion, reduced the percentage of infarct area in the ventricle, and effectively decreased prothrombin time (PT) and clotting time (TT) in serum[99]. *In vivo* experiments confirmed that the therapeutic potential of CF in MIRI was mediated by blocking the MAPK and NF-κB signaling pathways, inhibiting oxidative stress, and regulating the inflammatory cytokines.

Table 5

Volatile constituents from *Choerospondias axillaris*

No.	Compound name	Molecular formula	Extraction part
Alcohols			
V1	Ethanol	C_2H_6O	Wood
V2	2-Ethyl-1-hexanol	$C_8H_{18}O$	Wood
V3	Acetic acid	$C_2H_4O_2$	Wood
V4	Cyclohexanetetrol	$C_6H_{12}O_4$	Fruits
V5	6-Oxa-bicyclo[3.1.0]hexan-3-ol	$C_5H_8O_2$	Fruits
V6	γ-Eudesmol	$C_{15}H_{26}O$	Fruits
V7	2-Naphthalenemethanol, decahydro-à,à,4a-trimethyl-8-methylene-, [2*R*-(2à,4aà,8aá)]-	$C_{15}H_{26}O$	Fruits
V8	6-Isopropenyl-4,8a-dimethyl-1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-ol	$C_{15}H_{24}O$	Fruits
V9	1-(2-Butoxyethoxy)ethanol	$C_8H_{18}O_3$	Fruits
V10	2,2,4-Trimethyl-1,3-pentanediol	$C_8H_{18}O_2$	Fruits
V11	Cedrol	$C_{15}H_{26}O$	Fruits
Aldehyde ketone			
V12	Hexanal	$C_6H_{12}O$	Wood
V13	Octanal	$C_8H_{16}O$	Wood
V14	Nonanal	$C_9H_{18}O$	Wood
V15	Decanal	$C_{10}H_{20}O$	Wood
V16	Acetic anhydride	$C_4H_6O_3$	Fruits
V17	2-Butenal	C_4H_6O	Fruits
V18	1-Hydroxy-2-propanone	$C_3H_6O_2$	Fruits
V19	Furfural	$C_5H_4O_2$	Fruits
V20	4-Hexen-2-one	$C_6H_{10}O$	Fruits
V21	2(5H)-Furanone	$C_4H_4O_2$	Fruits
V22	2-Cyclopenten-1-one, 2-hydroxy-	$C_5H_6O_2$	Fruits
V23	1,2-Cyclopentanedione, 3-methyl-	$C_6H_8O_2$	Fruits
Alkenes			
V24	2,6,6-Trimethyl-(ñ)-Bicyclo[3.1.1] hept-2-ene	$C_{10}H_{16}$	Wood
V25	Limonene	$C_{10}H_{16}$	Wood
V26	Bicyclo[5.3.0]decane, 2-methylene-5-(1-methylvinyl)-8-methyl-	$C_{15}H_{24}$	Fruits
V27	à-Guaiene	$C_{15}H_{24}$	Fruits
Aromatics			
V28	Toluene	C_7H_8	Wood
V29	o-Xylene	C_8H_{10}	Wood
V30	Ethylbenzene	C_8H_{10}	Wood
V31	1,3-Dimethyl-benzene	C_8H_{10}	Wood
V32	Benzaldehyde	C_7H_6O	Wood
V33	Acetophenone	C_8H_8O	Wood
V34	1-Methylene-1H-indene	$C_{10}H_8$	Wood
V35	Butylated hydroxytoluene	$C_{15}H_{24}O$	Wood
V36	Dibenzofuran	$C_{12}H_8O$	Wood
V37	Phenol	C_6H_6O	Fruits
V38	Phenol, 2-methyl-	C_7H_8O	Fruits
V39	p-Cresol	C_7H_8O	Fruits
V40	Phenol, 2-methoxy-	$C_7H_8O_2$	Fruits
V41	Creosol	$C_8H_{10}O_2$	Fruits

(*Continued*)

Table 5
(Continued)

No.	Compound name	Molecular formula	Extraction part
V42	Phenol, 4-ethyl-2-methoxy-	$C_9H_{12}O_2$	Fruits
V43	2-Methoxy-4-vinylphenol	$C_9H_{10}O_2$	Fruits
V44	Phenol, 2,6-dimethoxy-	$C_8H_{10}O_3$	Fruits
V45	Phenol, 2-methoxy-4-(1-propenyl)-, (Z)-	$C_{10}H_{12}O_2$	Fruits
V46	1,2,4-Trimethoxybenzene	$C_9H_{12}O_3$	Fruits
V47	*trans*-Isoeugenol	$C_{10}H_{12}O_2$	Fruits
V48	5-*tert*-Butylpyrogallol	$C_{10}H_{14}O_3$	Fruits
V49	Benzene, 1,2,3-trimethoxy-5-(2-propenyl)-	$C_{12}H_{16}O_3$	Fruits
V50	3',5'-Dimethoxyacetophenone	$C_{10}H_{12}O_3$	Fruits
V51	Phenol, 2,6-dimethoxy-4-(2-propenyl)-	$C_{11}H_{14}O_3$	Fruits
V52	Ethanone, 1-(4-hydroxy-3,5-dimethoxyphenyl)-	$C_{10}H_{12}O_4$	Fruits
V53	Benzene, 1,1'-(1-Methylethylidene)bis[4-methoxy-	$C_{17}H_{20}O_2$	Fruits
V54	2,4-Di-tert-butylphenol	$C_{14}H_{22}O$	Fruits
V55	1,2-Benzenedicarboxylic acid	$C_8H_6O_4$	Fruits
Esters			
V56	2-Methyl-propanoic acid,1-(1,1-dimethylethyl)-2-methyl-1,3-propanediyl ester	$C_{16}H_{30}O_4$	Wood
V57	1,2-Ethanediol, monoacetate	$C_4H_8O_3$	Fruits
V58	Propanoic acid, 2-oxo-methyl ester	$C_4H_6O_3$	Fruits
V59	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	$C_{16}H_{30}O_4$	Fruits
V60	Dimethyl phthalate	$C_{10}H_{10}O_4$	Fruits
V61	Methyl tetradecanoate	$C_{15}H_{30}O_2$	Fruits
V62	Phthalic acid, butyl hex-3-yl ester	$C_{18}H_{26}O_4$	Fruits
V63	Dibutyl phthalate	$C_{16}H_{22}O_4$	Fruits
Organic acid			
V64	Hydroxyacetic acid	$C_2H_4O_3$	Fruits
V65	Acetic acid	$C_2H_4O_2$	Fruits
V66	*cis*-Vaccenic acid	$C_{18}H_{34}O_2$	Fruits
V67	Propanoic acid, 2-methyl-, 3-	$C_4H_8O_2$	Fruits
Others			
V68	Carbamic acid, monoammonium salt	$CH_6N_2O_2$	Fruits
V69	Ammonium acetate	$C_2H_7NO_2$	Fruits
V70	Furan, 2,5-dimethyl-	C_6H_8O	Fruits
V71	Tolycaine	$C_{15}H_{22}N_2O_3$	Fruits
V72	2-Propenamide, N-(aminocarbonyl)-	$C_4H_6N_2O_2$	Fruits
V73	N-Butyl-tert-butylamine	$C_8H_{19}N$	Fruits
V74	1,3,5-Cycloheptatriene, 1-methoxy-	$C_8H_{10}O$	Fruits
V75	Diepicedrene-1-oxide	$C_{15}H_{24}O$	Fruits
V76	Tricyclo[4.4.0.0(2,7)]dec-8-ene-3-methanol, à,à,6,8-tetramethyl-,stereoisomer		Fruits
V77	Formamide, N,N-dibutyl-	$C_9H_{19}NO$	Fruits
V78	Ethanol, 2-(2-butoxyethoxy)-,	$C_8H_{17}K_2O_6P$	Fruits

Anti-arrhythmic

Arrhythmias is one of the most serious heart diseases that occur in most heart diseases, which can increase the risk of sudden death in patients[121]. Ischemic heart disease and cardiac failure are the two major reasons that result in arrhythmias. Pharmacological study revealed that the condition of abnormalities in cardiac ion channels, or excitability, conduction, and automaticity abnormalities of heart which due to the gene mutations of channel proteins, usually disrupt myocardial electrical signal transmission then lead to arrhythmias[122]. However, these symptoms could be improved by CF total flavonoids. Previous study demonstrated that TFC can reduce Ca^{2+} concentration in myocardial cells in healthy rats[102],

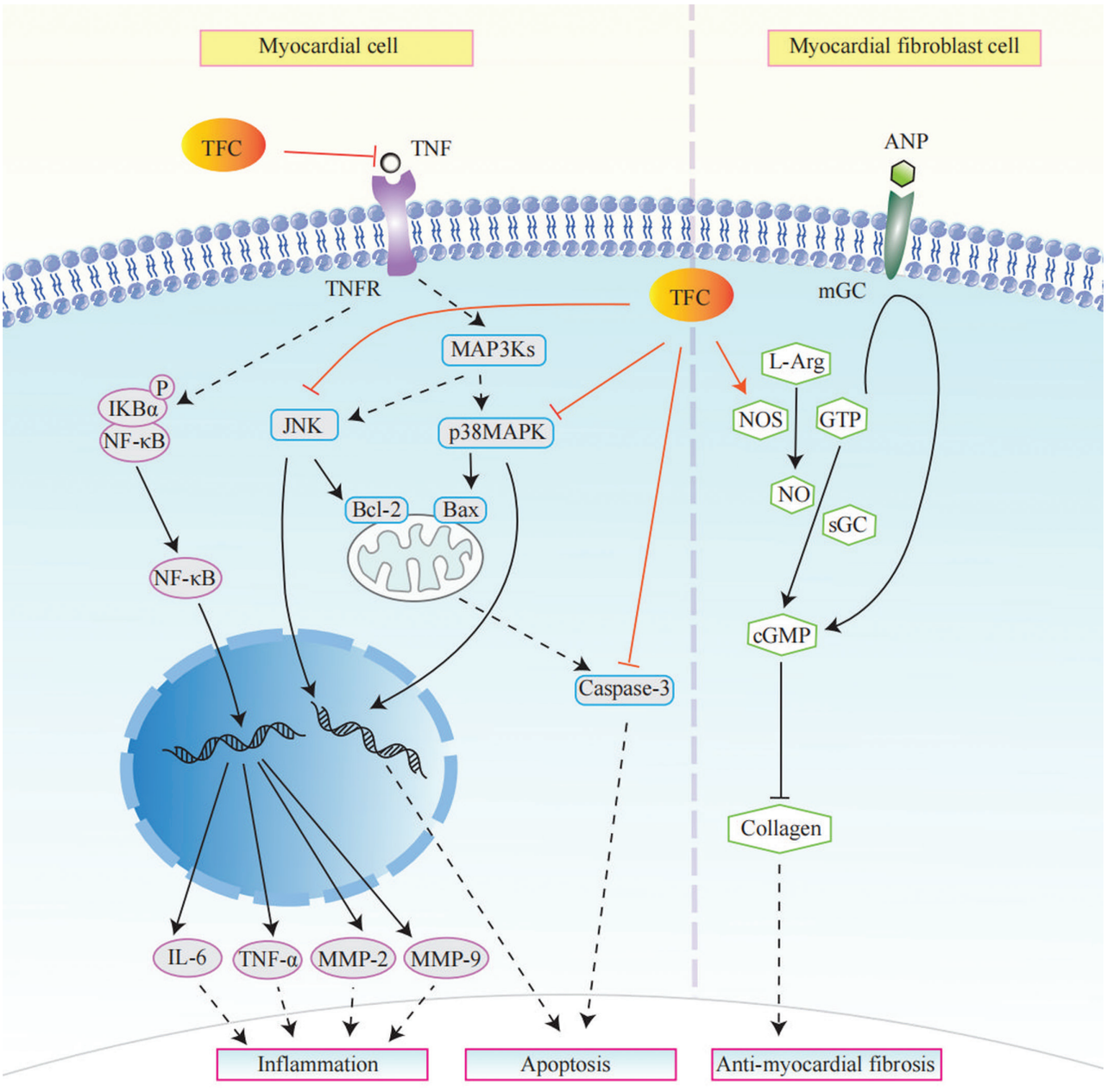


Figure 5. Pharmacological mechanism of *Choerospondias axillaris* in cardiovascular disease. ANP: Atrial natriuretic peptide; Bcl: B-Cell lymphoma; cGMP: Cyclic guanosine monophosphate; GTP: Guanosine triphosphate; IKBα: Inhibitory subunit of NF-κBα; IL: Interleukin; JNK: c-jun N-terminal kinase; MMP: Matrix metalloproteinase; NO: Nitric oxide; NOS: Nitric oxide synthase; NK-κB: Nuclear factor-kappa B; MAPK: Mitogen-activated protein kinase; mGC: Membrane-bound guanylate cyclase; sGC: Soluble guanylate cyclase; TFC: Total flavonoids of *C. axillaris* fruits; TNF: Tumor necrosis factor; TNFR: Tumor necrosis factor receptor.

and shorten the occurrence time of ventricular premature beats, VT, VF, and cardiac arrest in the arrhythmias model rats induced by aconitine[104]. On the other hand, TFCL significantly reduced the duration of VT and VF in rats in an ischemia-reperfusion model, revealing that TFCL presented a significant effect of alleviating ischemia-induced arrhythmias[101].

Anti-myocardial fibrosis

Myocardial fibrosis is a significant pathological condition in many cardiovascular diseases, such as arrhythmias, myocardial infarction, chronic heart failure, and impaired cardiac contractility, which leads to the increase of myocardial stiffness, decrease of cardiac contractility, and reduction of coronary flow reserve[123]. NO is a biological factor produced in almost all tissues and organs, which plays an important role in cardiovascular homeostasis[124]. It is released through the catalysis of nitric oxide synthase (NOS) from L-arginine (L-Arg), which stimulates the formation of cyclic guanosine monophosphate (cGMP) in the vascular smooth muscle cells, relaxing vascular smooth muscle, regulating vascular pressure, organ blood flow, and blood pressure[125]. Therefore, the signaling pathway associated with NO was an important indicator for myocardial fibrosis evaluation. Pharmacological research indicated that TFC significantly inhibited the synthesis of collagen in rat's

Table 6

Pharmacological activities of *Choerospondias axillaris*

Pharmacological effects	Compound or extract	Assay (subject and treatment)	Effect	Reference
Anti-myocardial ischemia and ischemia-reperfusion injury	TFC	Acute experimental myocardial ischemia model of rat, half male and half male, 5.0, 11.2 mg/kg, iv, *in vivo*	TFC can significantly resist the heart rate slowing effect caused by pituitary hormone and shorten the heart rate recovery time.	[96]
	TFC	Acute myocardial ischemia-reperfusion injury model of SD rat, 75, 150, 300 mg/kg, ig, *in vivo*.	The concentration of CAT ↑, GSH-Px ↑, SOD ↑, and MDA ↓. few apoptotic cell nuclei were confirmed in TUNEL assay, the expressions of Bax ↓ and caspase-3 ↓, Bcl-2 ↑. The expressions of MAPK ↓ and JNK ↓.	[97]
	TFC	Acute myocardial ischemia-reperfusion injury model of rat, 75, 150, 300 mg/kg, ig, *in vivo*.	The concentration of TNF-α ↓, IL-6 ↓, IL-10 ↑, and the expressions of MMP-2 ↓, MMP-9 ↓, TGF-β1 ↓, p-IKBα ↓.	[98]
	Simulated total organic acids	Acute myocardial ischemia-reperfusion injury model of rat, 0.5 g/kg, *in vivo*. Hypoxia-reoxygenation injury model of neonatal rat cardiomyocytes.	Reduce myocardial infarct size and infarct percentage. The content of coagulation parameters of PT ↓, TT ↓, Fib ↑, and the concentration of LDH ↓.	[99]
	Ethanol extract	Acute experimental myocardial ischemia model of rat, 5.6, 11.2, 22.4 mg/kg, iv, *in vivo*.	Reduce the size of myocardial ischemic infarction, improving rat ECG waveforms. The concentration of CK ↓, LDH, GOT ↓, ET ↓, NO ↑, NOS ↑.	[31]
	TFC	Experimental myocardial ischemia model of rat, 23 g (crude drug concentration)/kg, iv, *in vivo*.	The protein with the molecular weight of 6,736 u and 10,141 u were highly expressed; and the protein with the molecular weight of 4,012 u, 5,239 u, 7,426 u, 8,681 u, 17,627 u were lowly expressed.	[100]
	TFCL	Experimental myocardial ischemia model of rat, 0.1, 0.4 g/kg, iv, *in vivo*.	VT↓, VF↓, the concentration of CK ↓, TNF-α ↓, IL-6 ↓, NF-κB ↓, NO ↑.	[101]
Anti-arrhythmic	TFC	Clinical healthy Wistar rat, 6, 12, 24, 48 mg/kg, i.g., *in vivo*.	Ca^{2+} ions ↓ in a dose-dependent manner.	[102]
	TFC	Isolated right ventricular papillary muscle of guinea pig, 1% TFC aqueous solution, 0.1, 0.3, 0.5, 0.7 mL, *in vitro*	The papillary muscles were weakened with the treatment of TFC in a dose-dependent manner. Extracellular Ca^{2+} ions ↓ in a dose-dependent manner.	[103]
	TFCL	Myocardial ischemia-reperfusion injury model SD rat, 0.1, 0.4 g/kg, *in vivo*.	VT and VF ↓, CK ↓, and the concentration of TNF-α ↓, IL-6 ↓ and NF-κB ↓, NO ↑, reduction in infarcted myocardial tissue, ventricular mass, and infarct size.	[101]
	TFC	Isolated arrhythmia model of rat, aconitine-induced arrhythmia model of Wistar rat.	Prolong the occurrence time of premature beats, VT, VF, and cardiac arrest of arrhythmia model rat in a dose-dependent manner.	[104]
Anti-myocardial fibrosis	TFC	Ang II-induced SD rat cardiac fibroblasts fibrosis model, 25, 50, 100 mg/L of TFCF, *in vitro*.	50 and 100 mg/L TFC groups significantly inhibited the proliferation and collagen synthesis of rat cardiac fibroblasts.	[105]
	TFC	Ang II-induced SD rat cardiac fibroblasts fibrosis model, 25, 50, 100 mg/L of TFC, *in vitro*.	Collagen synthesis was inhibited, and these effects were blocked by pretreatment with L-NAME or ODQ. NO ↑, NOS ↑, and cGMP ↑.	[106]
Hemorheological effect	TFC	Healthy rabbit, half male and half male, 20 mg/kg, ig., *in vivo*.	Whole blood-specific viscosity ↓, plasma-specific viscosity ↓, packing volume ↓, erythrocyte sedimentation rate ↓.	[107]

(*Continued*)

Table 6
(Continued)

Pharmacological effects	Compound or extract	Assay (subject and treatment)	Effect	Reference
	Compound Guangzao injection	ADP-induced rabbit and rat platelet aggregation, 0.586, 1.172 g/kg, iv., *in vivo*.	Significantly inhibited platelet aggregation in rabbit and rat, the time of carotid artery thrombosis ↑.	[108]
Antioxidant	Aqueous extract	D-galactose induced male Kunming mice aging model for *in vivo* assay, and superoxide anions, DPPH, H_2O_2, OH for *in vitro* assay.	The concentration of SOD ↑, MDA ↓, and inhibited the reduction of GSH ↓, GSH-px ↓. IC_{50}/DPPH = 0.53 mg/mL. IC_{50}/OH^- = 7.45 mg/mL, IC_{50}/O^{2-} = 0.10 mg/mL. H_2O_2-scavenging activity was 32.8% at the concentration of 20 mg/mL. Reducing power was 0.60 at 0.62 mg/mL. The chelating rate of Fe^{2+}-chelating activity at the concentration of 0.31 mg/mL was 86.4%.	[66]
	PAs	DPPH, ABTS, reducing power, cellular antioxidant detected by Caco-2 cells and HUVECs, and anti-angiogenic effects *in vitro*.	IC_{50}/DPPH = 164 μg/mL, IC_{50}/ABTS = 154 μg/mL, potent reducing power was 0.930 g AAE/g, and cellular antioxidant activity EC_{50} = 10.2 and 38.9 μg/mL without or with PBS wash, respectively.	[11]
	Phenolic composition of *C. axillaris* peels (PP) and fleshes (FP)	Ferric-reducing antioxidant power, total antioxidant activity, DPPH scavenging ability *in vitro* assay.	PP (IC_{50}/DPPH 91.46 μg/mL), FP (IC_{50}/DPPH 134.13 μg/mL). Total antioxidant capacities equivalent to 0.73 (PP) and 0.59 mg (FP) ascorbic acid. Ferric-reducing antioxidant power: PP > FP. PP antimicrobial effect: PP > FP. The IC_{50} HepG2 inhibiting rate: IC_{50} = 39.31 μg/mL (PP) and 47.49 μg/mL (FP). Caco-2 cells inhibiting rate: 101.90 μg/mL (PP) and 102.61 μg/mL (FP).	[65]
	Flavonoid fractions from *C. axillaris* Fruits (F1 and F2)	DPPH radical, total antioxidant capacity, hydroxyl radical, and superoxide anion radical scavenging activities	DPPH radical scavenging activity: F1 and F2 > VC. For the total antioxidant capacity and superoxide anion radical scavenging activity: F1 and F2 < VC.	[109]
	TFC	Adriamycin-induced rat myocardiac peroxidation injury model, 100, 150, 200 mg/kg, i.g., *in vivo*	The concentration of LDH ↓, AST ↓, CK ↓, MDA ↓, and SOD ↑, GSH-Px ↑. Myocardial peroxidative injury can be inhibited.	[110]
	Polysaccharides from *C. axillaris* fruits (CALP-60 and CALP-80, and CALP-S)	DPPH-free radical and hydroxyl radical scavenging, reducing power.	The antioxidant activities: CALP-S > CALP-60 and CALP-80.	[111]
	Polysaccharides from *C. axillaris* leaves	Ferric-reducing antioxidant power, DPPH, hydroxyl radical scavenging activity.	Crude polysaccharide was stronger than that of pure polysaccharide at the concentration of 0.20–0.8 mg/mL. IC_{50}/DPPH = 0.79 mg/mL and 1.06 mg/mL of CALP-1 and CALP-2.	[13]
	TFCL	Ferric-reducing antioxidant power, and DPPH.	The scavenging ability of DPPH was 92% at the concentration of 0.12 mg/mL and reducing power of Fe^{3+} was 94% at the concentration of 0.6 mg/mL.	[112]
	Ethyl acetate, acetone, methanol, and water extract	DPPH, xanthine oxidase	Acetone extract exhibited the highest antioxidant activity, IC_{50}/DPPH = 15.72 μg/mL; inhibition of xanthine oxidase, IC_{50} = 20.80 μg/mL.	[12]
Anti-inflammatory	Methanol extract	CIA female Wistar rat model, 300 mg/kg, p.o., orally, *in vivo*. Trauma primary cells, 5 mg/mL, 24 h, *in vitro*.	The concentration of TNF-α ↓, IL-6 ↓. Total 27% decrease in paw volume. Methanol extract exhibited protection against bone resorption and reduction in soft tissue *in vivo*.	[3]

AAE: Ascorbic acid equivalents; ABTS: 2,2'-Azinobis(3-ethyl-2,3-dihydro-, diammonium salt); ANG-II: Angiotensin II; AST: Aspartate aminotransferase; Bax: Bcl-2-associated X protein; Bcl-2: B-Cell lymphoma-2; CALP: *choerospondias axillaris* leaf polysaccharides; CAT: Catalase; cGMP: Cyclic guanosine monophosphate; CIA: Collagen-induced arthritis; CK: Creatine kinase; DPPH: 2,2-Diphenyl-1-picrylhydrazyl; ECG: Electrocardiogram; ET: Endothelin; Fib: Fibrinogen; GOT: Glutamic oxaloacetic transaminase; GSH-Px: Glutathione peroxidase; HUVECs: Human umbilical vein endothelial cells; IC_{50}: Half maximal inhibitory concentration; ig: Intragastric; IL: Interleukin; iv: Intravenous; JNK: c-jun N-terminal kinase; LDH: Lactate dehydrogenase; L-NAME: Nitro-L-arginine methyl ester; MAPK: Mitogen-activated protein kinase; MDA: Malonaldehyde; MMP: Matrix metalloproteinase; NF-κB: Nuclear factor-kappa B; NO: Nitric oxide; NOS: Nitric oxide synthase; ODQ: 1H-[1,2,4] oxadiazolo[4,3-a]quinoxalin-1-one; PBS: Phosphate-buffered saline; p-IKBα: Phosphorylation inhibitory subunit of NF-κBα; PAs: Proanthocyanidins; PT: Prothrombin time; SD: Sprague-Dawley; SOD: Superoxide dismutase; TFC: Total flavonoids of C. axillaris fruits; TFCF: Total flavones from Chorspondiatis Fructus; TFCL: Total flavonoids of C. axillaris leaves; TGF-β: Transforming growth factor-β; TNF-α: Tumor necrosis factor-α; TT: Clotting time; TUNEL: Terminal deoxynucleotidyl transferase dUTP nick-end labeling; VC: Vitamin C; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

myocardial fibroblasts and cardiac fibroblasts, led to an increase in the level of NO, NOS, and cGMP. Hence, the NO-cGMP signaling pathway was a proposed mechanism of CF inhibiting myocardial fibrosis[105–106].

Hemorheological effect

Thrombus formation and platelet aggregation were two of the pathogenesis of coronary heart disease, which led to fibroblast proliferation, vasoconstriction, and inhibition of thrombolysis, then increasing the risk of coronary heart disease[126]. Some studies have shown that TFC could inhibit platelet aggregation in normal rabbits rapidly and had a sustained effect. Meanwhile, the whole blood viscosity at high and low shearing and blood plasma viscosity were obviously reduced, and also the hematocrit and the erythrocyte sedimentation rate were significantly decreasing. Furthermore, TFC increased the blood flow and improved the blood circulation and microcirculation in normal rabbits[107]. On the other hand, the compound Guangzao injection significantly inhibited rabbits' platelet aggregation induced by adenosine diphosphate (ADP) *in vitro*, and this inhibitory effect is dose-dependent. Additionally, the study in the experimental rats thrombosis model which was induced by electrical stimulation of the carotid artery demonstrated that compound Guangzao injection significantly prolonged the time of carotid artery thrombus formation and exhibited an obviously inhibitory effect on ADP-induced platelet aggregation in rats, indicating that CF has a role in enhancing systemic blood circulation and improving microcirculation[108].

Antioxidant

Oxidative stress is highly related to cardiovascular risk, which plays an important role in the onset and progression of atherosclerosis, and impacts the development of cardiovascular events[127]. CF has traditionally been used for cardiovascular diseases that are related to oxidative stress[128]. High contents of flavonoids and phenolics are the material basis for its antioxidant activity[66]. The aqueous extract, proanthocyanidins, phenolic composition, and flavonoid fractions from CF exhibited significant 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 6-benzothiazolesulfonic acid, 2,2'-azinobis(3-ethyl-2,3-dihydro-, diammonium salt) (ABTS) radical scavenging activities, total antioxidant activity, ferric-reducing antioxidant power, and so on, and the antioxidant activity increased with the concentration of total flavonoids and total phenols[11,65–66,109]. Furthermore, crude polysaccharides from *C. axillaris* fruits and leaves were found to have antioxidant activities stronger than those of pure polysaccharides, and these results may be due to the presence of flavonoids or phenolics in the crude polysaccharides[13,111].

Anti-inflammatory

Earlier reports showed that the scavenging oxidative stress of antioxidant compounds reduced the risk of inflammation[129–130]. In a recent study, a methanol extract of CF showed significant anti-inflammatory effects. Methanol extract (300 mg/kg) exerted anti-inflammatory effects on a collagen-induced arthritis (CIA) female Wistar rat model. The levels of the inflammatory cytokines TNF-α and IL-6 were significantly reduced in rheumatoid arthritis (RA) rat model *in vitro*, with a total 27% decrease in paw volume. Methanol extract of CF exhibited reduced inflammation of inflammatory diseases[3].

In conclusion, the extract of *C. axillaris* in different parts exhibited a variety of pharmacological activities of cardiovascular disease. For further development and clinical application, the pharmacodynamic material basis and pharmacological mechanisms should be further defined.

Pharmacodynamic material basis

Given the complexity and multifaceted efficacy of TCM components, it is essential to identify chemical compounds for the treatment of cardiovascular diseases of *C. axillaris*, Zhang et al.[54] isolated the active fraction responsible for its anti-arrhythmic effect, and six compounds were collected from the active fraction. They were β-sitosterol, quercetin, kaempferol, protocatechuic acid, gallic acid, and vanillic acid. These six compounds were suggested to be potential active substances contributing to the anti-arrhythmic effects of *C. axillaris*. Wang et al.[58] used ADP-induced platelet aggregation as an indicator and traced and separated the blood-activating and effective constituents of *C. axillaris* fruit ethanol extract. They identified the blood-activating compounds of *C. axillaris* fruit, which include protocatechuic acid, gallic acid, 3,3′-di-*O*-methylellagic acid, ellagic acid, citric acid, and hydroquinone. Furthermore, Chi et al.[131–133] employed affinity fishing technology with coronary artery disease-related enzymes to study the active compounds of *C. axillaris* fruit in treating coronary cardiovascular diseases, including COX-2, peroxisome proliferator-activated receptor γ (PPAR-γ), and angiotensin-converting enzyme (ACE), and the active compounds were identified by ultraperformance liquid chromatography plus Q-Exactive Orbitrap tandem mass spectrometry (UHPLC-Q-Exactive Orbitrap-MS/MS). For COX-2, they identified 21 ligands, including seven phenolic acids (protocatechualdehyde, protocatechuic acid, vanillic acid, gallic acid, caffeic acid, ellagic acid, and isovanillin), seven flavonoids (pinocembrin, naringenin, kaempferol, catechin, quercetin, taxifolin, and rutin), four organic acids (succinic acid, quinic acid, citric acid, and palmitic acid), and three other compounds (hydroquinone, syringaldehyde, and pantothenic acid). For PPAR-γ, they identified 16 ligands, including four phenolic acids (vanillic acid, protocatechuic acid, protocatechualdehyde, and caffeic acid), six organic acids (quinic acid, succinic acid, malic acid, palmitic acid, stearic acid, and linoleic acid), five flavonoids (catechin, hyperin, taxifolin, naringenin, pinocembrin), and one other compound (balanophonin). For ACE, they identified three active ligands (quercetin, isorhamnetin, and quinic acid). These findings demonstrated that phenolic acids, organic acids, and flavonoids were the material basis for the efficacy in treating cardiovascular diseases of *C. axillaris* fruit.

Conclusion and perspectives

C. axillaris is an edible fruit tree with significant medicinal value, especially in treating cardiovascular diseases. In summary, we comprehensively reviewed the traditional applications and modern research findings related to *C. axillaris*, including its use in traditional application, phytochemistry, pharmacological research of cardiovascular protection, and pharmacodynamic material basis. Although great progress has been made in the research of *C. axillaris* over recent decades, there are some challenges that need further research.

First, while more than 70 chemical constituents have been identified and confirmed in *C. axillaris*, other types of active substances, such as oligosaccharides, polysaccharides, and exosomes should be conducted to expand the new medicinal resources and provide more chemical character to illustrate the pharmacodynamic material basis.

Preliminary studies on *C. axillaris* polysaccharides presented significant antioxidant activity *in vitro*, indicating that polysaccharides may be one of the active components of *C. axillaris*. For the complex structure with a large molecular weight of polysaccharides, which still a challenge to analyze its complete chemical structure. Therefore, in-depth research on isolation, identification methods, and bioactivity evaluation can be further explored. Currently, modern research has shown that oligosaccharides and exosomes are also essential active substances in medicinal plants. However, there has been no research related to oligosaccharides and exosomes from *C. axillaris*. Hence, further study is needed for the extraction, identification, and investigation of the pharmacological activity of *C. axillaris* oligosaccharides and exosomes.

On the other hand, the weak pharmacological research on *C. axillaris* that makes it difficult to explain the pharmacological mechanistic of remarkable cardiovascular diseases therapeutic effects, which results in the in-depth pharmacological mechanistic studies and target investigations are still lacking. In the future, systematic biology techniques such as metabolomics, proteomics, and transcriptomics can be employed deeper into the pharmacological mechanisms study of *C. axillaris*. Additionally, the current pharmacological research on *C. axillaris* primarily focuses on extracts, and there is a need for more systematic studies to explain the pharmacological substance basis of *C. axillaris* and its relationship between individual compounds and therapeutic efficacy. As a TCM, the efficacy of CF is primarily documented in ancient medical works. Modern pharmacological studies have been conducted to elucidate the material basis and mechanism of action for pharmacological effects, yet clinical studies remain limited. Furthermore, CF is predominantly used in compound formulations rather than as a monotherapy, which may be one of the reasons for the lack of clinical research. Consequently, there is a shortage of clinical studies on CF.

In conclusion, further research holds the promise that *C. axillaris* is expected to be a valuable resource for developing new drugs for cardiovascular diseases and other diseases. To achieve this, deeper investigations should be conducted that aimed at identifying the pharmacodynamic material basis, elucidating its pharmacological mechanisms, conducting safety assessments, and enhancing quality control measures basis of treatment cardiovascular diseases of *C. axillaris*, so as to narrow the gaps in the knowledge of current and future research of *C. axillaris* health value, and give some enlightenment to translate traditional application into new food additive, new drugs and clinical application.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Yanfei Huang contributed to conceptualization, methodology, data curation, writing-original draft, writing-review and editing, and funding acquisition. Qi Ye contributed to visualization, data curation, investigation, and writing-original draft. Yifan Tian contributed to investigation, data curation, and writing-original draft. Li Yang contributed to formal analysis and data curation. Zhiyan Liu contributed to formal analysis and data curation. Liping Bai contributed to visualization and conceptualization. Yuan Liu contributed to conceptualization, supervision, and writing-original draft. Zhifeng Zhang, Weiyi Tian, and Pei Luo contributed to supervision and project administration.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

All relevant data are within the manuscript.

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