

# Botanical Influences on Cardiovascular Disease

by Alan L. Miller, N.D.

## Abstract

Several botanicals, including *Crataegus oxycantha*, *Terminalia arjuna*, *Inula racemosa*, and *Astragalus membranaceus*, have been found to have therapeutic benefit for the treatment of cardiovascular disease. *Crataegus oxycantha* has been used traditionally as a cardiac tonic and current uses include treatment for angina, hypertension, arrhythmias, and congestive heart failure. Animal studies have also indicated that *Crataegus* extracts may also have potential use as anti-ischemic and lipid-lowering agents. The bark of the *Terminalia arjuna* tree has a long history of use as a cardiac tonic as well, and has been indicated in the treatment of coronary artery disease, heart failure, hypercholesterolemia, and for relief of anginal pain. Additionally, it has been found to have antibacterial and antimutagenic properties. *Inula racemosa*, also known as Pushkarmoola, is another traditional Ayurvedic botanical that has potential cardioprotective benefit. In human trials, a combination of *Inula racemosa* and *Commiphora mukul* was shown to be superior to nitroglycerin in reducing the chest pain and dyspnea associated with angina. *Astragalus membranaceus*, a Chinese herb, is often used as a “Qi tonifier” and has been studied for its therapeutic benefit in treatment of ischemic heart disease, myocardial infarction, heart failure, and relief of anginal pain. Clinical studies have indicated that its *in vitro* antioxidant activity is the mechanism by which it affords its cardioprotective benefit.

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## Crataegus oxycantha—Anti-Ischemic Cardiotonic

### Introduction

The berries and flowers of the common Hawthorn (*Crataegus oxycantha* & *monogyna*), a member of the Rosaceae family, have been used traditionally as a cardiac tonic, and are widely used currently for conditions including angina, hypertension, arrhythmias, and congestive heart failure.

### Active Constituents

The main constituents of *Crataegus* are amines, triterpene saponins, flavonoids and their glycosides, catechin and epicatechin, and oligomeric proanthocyanidins (see Table 1 for a more

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*Crataegus oxycantha*

complete list). The primary cardioprotective activity of this plant is generally attributed to its flavonoid and oligomeric proanthocyanidin (OPC) content. Although numerous flavonoid molecules have been found to have positive effects on the cardiovascular system, it appears the combination of flavonoid-based constituents in *Crataegus* provides the beneficial cardiovascular activity known to this popular botanical.

**Flavonoids** are found in many foods and botanical medicines, appearing in fruits, flowers, leaves, bark, skin, and seeds. Many botanical medicines, including *Ginkgo biloba*, *Vaccinium myrtillus*, and *Silybum marianum* (milk thistle) owe their physiologic activity to their flavonoid content. Flavonoids have been shown to increase collagen cross-linking in the vascular endothelium, strengthening blood vessels, as well as having potent antioxidant activity. The French Paradox of a high fat diet, yet a decreased incidence of heart disease, is attributed to the intake of flavonoid substances in red wine. Recent epidemiological studies have found an association between dietary flavonoid intake and reduced risk of heart disease, myocardial infarction, and stroke.<sup>1,2</sup>

### Mechanisms of Action

*Crataegus*' cardiovascular effects appear to be primarily due to its inotropic and chronotropic effects, enhanced blood vessel integrity, and effects on coronary blood flow and oxygen utilization.

### Protection from Ischemia

Human neutrophil elastase (HNE), which is released by activated neutrophils in significantly greater amounts under ischemic conditions, may be partly responsible, along with free radicals, for myocardial damage in ischemia and reperfusion.<sup>3</sup> It has been suggested that the cardioprotective activity of *Crataegus* may be due to radical scavenging and inhibition of HNE by the oligo-

meric proanthocyanidin (OPC) fragment of the leaves and flowers. Chatterjee et al found radical scavenging and HNE inhibition in various fractions of a *Crataegus* extract, with the greatest activity in the OPC fraction. This should not be interpreted as stating other components of the extract are not important, just that the OPCs in this plant possess stronger radical scavenging activities and elastase inhibition than other constituents.<sup>4</sup>

Animal studies on one *Crataegus* flavonoid, monoacetyl-vitexin rhamnoside, have suggested it has potent anti-ischemic properties. It was found to exert vasodilatory action, mediated in part by endothelium-derived relaxing factor in addition to phosphodiesterase inhibition.<sup>5</sup>

It has been indicated that *Crataegus* extracts improve the energy dynamics of the heart muscle, especially in ischemic conditions. Animal studies showed lactic dehydrogenase (LDH) release from isolated hearts during ischemia and reperfusion was significantly decreased after pre-treatment with

**Table 1.** Chemical Constituents of *Crataegus oxycantha*

<b>Amines</b> b-phenethylamine tyramine acetylcholine	<b>Flavonoids and their Glycosides</b> quercetin hyperoside rutin vitexin isovitexin
<b>Triterpene Saponins</b> oleanolic acid ursolic acid crataegolic acid	orientin isorientin apigenin
<b>Catechins</b> catechin epicatechin	<b>Oligomeric Proanthocyanidins</b> various OPCs

*vitro*. Thromboxane A2 is a potent inflammatory mediator which also causes platelet aggregation.<sup>10</sup>

### **Anti-arrhythmia**

#### **Effects of Crataegus**

Many cardioactive drugs, including digoxin, shorten the refractory period of the myocardium, which can result in an increased risk of arrhythmias. In animal studies, Crataegus extract had the opposite effect, prolonging the

refractory phase and potentially reducing the risk of arrhythmias.<sup>11,12</sup>

### **Crataegus & Lipid Metabolism**

Evidence from animal studies suggests Crataegus might also have a positive effect on blood lipids, although more research in this area is needed. Rats which were fed a diet known to be hyperlipidemic were then given a liquid tincture of Crataegus, resulting in decreased blood levels of cholesterol and triglycerides. The extract also inhibited fat deposition in the aorta and liver.<sup>13</sup>

In another study, rats fed an atherogenic diet had significantly increased plasma cholesterol, hepatic and fecal bile acids, and decreased hepatic cholesterol biosynthesis. Oral administration of a Crataegus tincture caused statistically significant reductions in total cholesterol and hepatic cholesterol biosynthesis, as well as significant increases in hepatic and fecal bile acids compared to rats fed the atherogenic diet or a normal diet. Since *de novo* hepatic cholesterol synthesis was further decreased in the treatment group, there was more emphasis on degradation of LDL cholesterol for the increased bile acid production. This is further suggested by the up-regulation of hepatic LDL receptors in this group.<sup>14</sup>

Crataegus, suggesting a protective effect of the extract on the myocardium.<sup>6</sup>

A similar study of the effect of Crataegus on isolated rat hearts in ischemia and reperfusion revealed significant improvements in mechanical functioning of the heart compared to controls (which suffered irreversible damage) during this process, without an increase in coronary flow. Again, this indicates more efficient myocardial energy utilization.<sup>7</sup>

An interesting animal study of Crataegus flavonoids revealed that different flavonoid constituents have differing effects on the heart, some increasing coronary flow, left ventricular pressure, and heart rate, and others not affecting these parameters, or even decreasing them. This is not unexpected, as this type of balanced effect is seen in many plant species.<sup>8</sup>

A preparation of isolated flavonoids from Crataegus caused increased coronary blood flow in rabbits, with a decrease in oxygen consumption by the myocardium and a reduction in coronary spasm. It also increased the pumping action of the heart and reduced the heart rate.<sup>9</sup>

Crataegus tincture and isolated flavonoids from Crataegus have also been found to inhibit the formation of thromboxane A2 *in*

## Crataegus Extract in Congestive Heart Failure

Because of its known positive effects on cardiac function, Crataegus extract was studied for its effect *in vivo* on congestive heart failure. In a multicenter, double-blind study, 136 patients with cardiac insufficiency, diagnosed as class II utilizing New York Heart Association (NYHA) criteria (this is characterized by reduced cardiac output and increased symptomatology with medium effort), were treated with a Crataegus extract or placebo for eight weeks. A total of 129 patients finished the trial. The primary objective study parameter—the pressure rate/product difference (PRP) (which is calculated by multiplying the heart rate by the systolic blood pressure and dividing by 100) is recognized as a standard direct measure of cardiac performance capacity. This evaluation is performed at rest, then after two minutes on a stationary bicycle at a specified exertion level. Evaluations were performed at the beginning of the trial and at eight weeks. A statistically significant improvement in cardiac function (by PRP) was noted in the Crataegus group over the eight-week period. The PRP in the placebo group, however, progressively deteriorated.

A secondary parameter of this study, the patients' subjective evaluation of their main complaints of reduced exercise performance, shortness of breath, ankle edema, and nocturia, was significantly improved in the test subjects vs. placebo. The participants' quality of life (which was mostly related to the mental-emotional state), was also improved in the Crataegus group, although not enough to be statistically significant compared to placebo. Crataegus extract was very well tolerated, and lab values (electrolytes, liver enzymes, cho-

lesterol, blood sugar) showed no relevant changes.<sup>15</sup>

In another double-blind, placebo-controlled study, 30 patients with NYHA stage II cardiac insufficiency were given Crataegus extract for eight weeks. A significant advantage was noted in the Crataegus group compared to placebo in post-exercise PRP, heart rate, and subjective patient symptomatology.<sup>16</sup> One capsule (80 mg) twice daily of a proprietary Crataegus extract standardized to contain 15 mg (approx. 18%) oligomeric proanthocyanidins was used in this and the previous study.

In his book, *Herbal Medicine*, R.F. Weiss suggests the following indications for Crataegus: 1) Patients with “degeneration of the cardiac muscle or coronary artery disease.” He states anginal symptoms of coronary artery disease can be treated successfully with Crataegus if given long-term; 2) Hypertension—primarily to improve cardiac function; 3) Weakness of the myocardium after infectious diseases and for muscular insufficiency in patients requiring digitalis, as it may optimize digitalis' effect; 4) Cardiac arrhythmias, mainly extrasystoles and tachycardia. Crataegus' effects as an antioxidant, in optimizing myocardial energy use, its anti-ischemic effects, and anti-arrhythmic effects occur over time; i.e. Crataegus does not work well in the treatment of acute angina, and thus it is considered to be a long-term treatment.<sup>17</sup>

### Indications for Crataegus

Angina  
Arrhythmias  
Congestive Heart Failure  
Coronary Artery Disease  
Hypertension  
Myocardial Weakness

## Terminalia arjuna—Ayurvedic Cardioactive Botanical

### Introduction

The bark of the *Terminalia arjuna* tree has been used in Ayurvedic medicine for over 2500 years, primarily as a “cardiac tonic.”

## *Terminalia arjuna*



Clinical research has indicated its usefulness in relieving anginal pain, and in the treatment of coronary artery disease, heart failure, and possibly hypercholesterolemia. It has also been found to be antibacterial and antimutagenic.

### **Active Constituents**

Terminalia's active constituents include tannins, triterpenoid saponins (arjunic acid, arjunolic acid, arjungenin, arjunglycosides), flavonoids (arjunone, arjunolone, luteolin), gallic acid, ellagic acid, oligomeric proanthocyanidins (OPCs), phytosterols, calcium, magnesium, zinc, and copper.

### **Mechanisms of Action**

Improvement of cardiac muscle function and subsequent improved pumping activity of the heart seem to be the primary benefits of Terminalia. It is thought that the saponin glycosides might be responsible for the inotropic effects of Terminalia, while the flavonoids and OPCs provide free radical antioxidant activity and vascular strengthening. Unlike Crataegus, Terminalia has not had the extensive studies of its constituents, and this type of study would be beneficial to the understanding of this botanical.

### **Clinical Studies on Terminalia**

An open study of Terminalia's effects on stable and unstable angina revealed a 50 percent reduction of anginal episodes in patients with stable angina ( $p < 0.01$ ) after three months' treatment. A statistically significant reduction was also noted in systolic blood pressure in these patients ( $p < 0.05$ ). On treadmill testing, both the time to onset of angina and the time to appearance of ECG ST-T changes were significantly increased in the stable angina group ( $p < 0.001$ ), indicating an improvement in exercise tolerance (Figure 1). The unstable angina patients in this study did not experience significant reductions in angina or systolic blood pressure. Both groups showed improvements in left ventricular ejection fraction. When these improvements were combined for statistical purposes, the improvements were significant ( $p < 0.05$ ). Evaluating the overall clinical condition, treadmill testing, and ejection fraction, 66 percent of the stable angina patients and 20 percent of the unstable angina patients improved during three months of therapy.<sup>18</sup>

### **Congestive Heart Failure**

Chronic congestive heart failure, with an annual mortality rate of more than 40

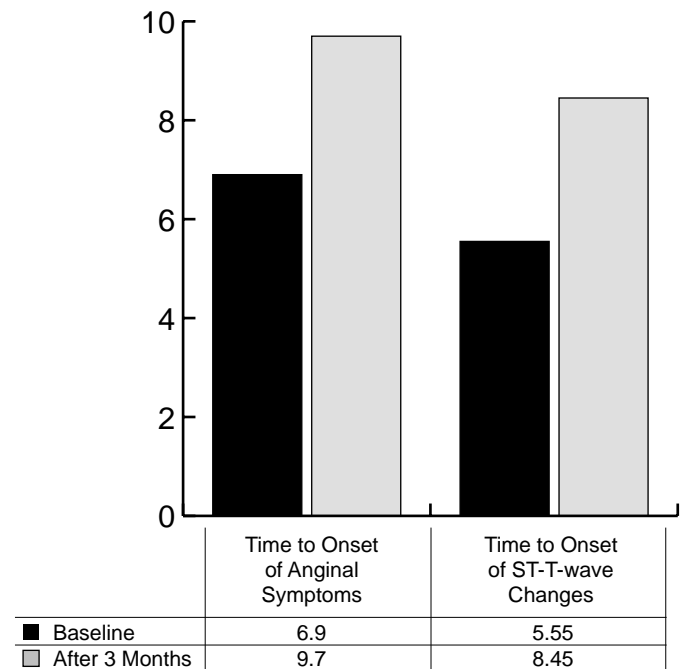
percent, can be a difficult condition to treat. Because of Terminalia's effect of increasing cardiac output, Indian researchers conducted a two-phase trial of Terminalia extract treatment in twelve patients with severe refractory heart failure (NYHA Class IV). Either 500 mg Terminalia bark extract or placebo was given every eight hours for two weeks in this double-blind study. All patients continued their drug therapy during the study. These included digoxin, diuretics, angiotensin-converting-enzyme inhibitors, vasodilators, and potassium supplementation. Symptoms of dyspnea, fatigue and edema improved while patients were on Terminalia therapy, and walking tolerance improved as well. All patients had dyspnea at rest or after minimal activity at the start of the trial. Echocardiographically, Terminalia therapy was associated with significant improvements in stroke volume and left ventricular ejection fraction, with decreases in end-diastolic and end-systolic left ventricular volumes compared to placebo. In the second phase of the study, patients from phase I were continued on Terminalia extract for approximately two years. Improvements were noted in the ensuing two to three months, and were maintained throughout the balance of the study. After four months of treatment, nine patients had improved to NYHA Class II and three improved to Class III. This was a significant piece of research, as these patients had not responded to conventional drug therapy, and yet had significant improvements in objective and subjective parameters while taking Terminalia.<sup>19</sup>

A subsequent study was conducted on 10 patients post myocardial infarction and two patients with ischemic cardiomyopathy, utilizing the same 500 mg every eight hours dosage as above, for three months. Patients were continued on conventional treatments. Significant reductions in angina, left ventricular ejection fraction, and left

ventricular mass were noted in the Terminalia group, whereas a control group taking only conventional drugs had decreased angina only. The two patients with cardiomyopathy improved from NYHA Class III to Class I during the study.<sup>20</sup>

Animal studies suggest Terminalia can reduce blood lipids. Rabbits were made to be hyperlipidemic by feeding them an atherogenic diet. Two groups were given a Terminalia extract orally, and one group was used as a placebo control group. The animals given Terminalia had a significant, dose-related decrease in total and LDL cholesterol, compared to placebo ( $p < 0.01$ ).<sup>21</sup> However, the amounts used (100 mg/kg and 500 mg/kg body weight) were very large, and it remains to be seen if these significant changes will be

**Figure 1.** Improvements In Exercise Tolerance At Baseline And After Three Months' Treatment With *Terminalia arjuna* Extract (Stable Angina Group) ( $p < 0.001$ ).<sup>18</sup>



seen in humans taking relatively smaller oral doses.

In a similar study, rats were fed cholesterol (25 mg/kg body weight) alone or with Terminalia bark powder (100 mg/kg) for 30 days. Terminalia feeding caused a smaller increase in blood lipids and an increase in HDL

## Inula racemosa—Anti-Ischemic Ayurvedic Botanical

Another traditional Ayurvedic botanical, which has potential beneficial effects on the cardiovascular system, is *Inula racemosa*, also known as Pushkarmoola. A member of the Compositae family, Inula grows in the hilly regions in the northwestern Himalayas. In Ayurvedic medicine, the root powder of this plant is indicated for angina and dyspnea.

### Active Constituents

At least four sesquiterpene lactones have been isolated from Inula, including alantolactone, isoalantolactone, dihydroalantolactone, and dihydroisoalantolactone. These chemicals are thought to be at least partially responsible for Inula's therapeutic qualities, along with beta sitosterol, daucosterol, and inulinolide.

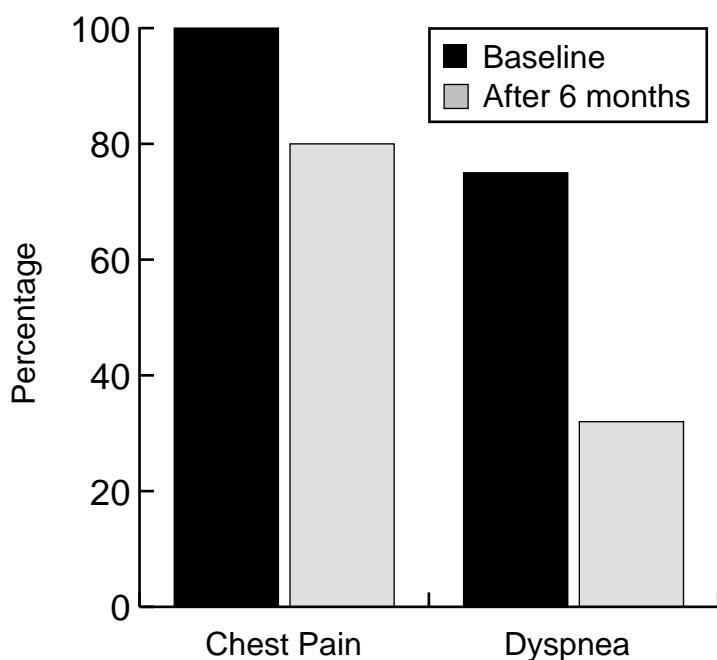
### Animal Research

Inula may have a cardioprotective effect, as demonstrated in rats given Inula before and after experimental myocardial infarction. Animals given Inula had smaller increases in SGOT, LDH, CPK, cAMP, cortisol, pyruvate, lactate, and glucose than those in an untreated control group.<sup>23</sup>

### Clinical Research

Inula was studied in combination with *Commiphora mukul* (a 1:1 mixture) in 200 patients with ischemic heart disease. Approximately 80 percent experienced dyspnea, and all 200 subjects had chest pain, with ST-segment and T-wave changes on electrocardiogram (ECG), suggestive of myocardial ischemia. Commiphora is known for its lipid-lowering qualities, so it is not surprising there

**Figure 2.** Percentage of Patients Experiencing Chest Pain and Dyspnea Before and After Treatment with Combination *Inula racemosa* and *Commiphora mukul*.<sup>24</sup>



cholesterol compared to the cholesterol-only group. The study's authors hypothesized that Terminalia's lipid-lowering effects were caused by inhibition of hepatic cholesterol biosynthesis, increased fecal bile acid excretion, and stimulation of receptor-mediated catabolism of LDL cholesterol, effects which mirror the lipid-lowering activity of Crataegus noted above.<sup>22</sup>

was a 39-percent decrease in total cholesterol, 51-percent decrease in triglycerides, and 32-percent decrease in total blood lipids. Patients were also instructed not to eat fried foods and “excessive carbohydrates,” which could have contributed to these findings. In addition, at the end of the six-month study period, 26 percent of the subjects had a complete restoration of normal ECG, while another 59 percent showed improvement in the ECG. Twenty-five percent of the subjects had no chest pain, and patients experiencing dyspnea fell to 32 percent, from a baseline 80 percent (Figure 2). Of those still experiencing chest pain and dyspnea, the subjective levels of pain also improved after treatment.<sup>24</sup>

The efficacy of *Inula* compared to nitroglycerin for the prevention of anginal symptoms was studied in nine subjects with ischemic heart disease. All patients experienced chest pain and ECG ST-segment depression (indicative of myocardial ischemia) on exertion. After pre-treatment with *Inula* (3 grams root powder 90 minutes prior to testing) or nitroglycerin, all nine subjects had improvement in ST-segment depression on ECG, with greater improvements seen after *Inula* treatment.<sup>25</sup>

### **Astragalus membranaceus— Cardioactive and Immunostimulatory Chinese Botanical**

*Astragalus membranaceus* is a Chinese herb often used as a “Qi tonifier” in the Oriental system of medicine. A great deal of the recent research on *Astragalus* has been on its immune-stimulating properties, as well as its effects on heart function. For a more complete review of this plant’s immune stimulatory effects, please refer to Sinclair’s review in vol 3(5) of this journal.<sup>26</sup>

### **Active Constituents**

*Astragalus* has been studied for its efficacy in ischemic heart disease, myocardial infarction, heart failure, in addition to its *in vitro* antioxidant activity. The root of the plant is used for medicinal purposes, and contains some unique flavones, including kumatakenin and 3’,7-dihydroxy-4’methoxyisoflavone, and their glucosides. *Astragalus*’ immunostimulatory properties lie in the polysaccharides present in the root. Also present are several saponins, called *Astragalosides* I to X.

### **Animal Research**

In an *in vitro* study, *Astragalus* was found to inhibit lipid peroxidation by 40 percent in a rat heart mitochondrial suspension.<sup>27</sup> Antioxidant activity is common to flavonoids, and is hypothesized to be an integral component of the cardioprotective activity of other plants, including *Crataegus*.

### **Clinical Studies**

Antioxidant activity was suggested as one of the mechanisms of *Astragalus*’ cardio- tonic action in a study of 43 patients given *Astragalus* after acute myocardial infarction. *Astragalus* significantly improved left ventricular function compared to controls.<sup>28</sup>

Twenty individuals with angina were treated for two weeks with *Astragalus*, and demonstrated a significant ( $p < 0.01$ ) improvement in cardiac output via echocardiogram.<sup>29</sup> In another angina study, 92 individuals with ischemic heart disease who were treated with *Astragalus* experienced marked improvement in angina, as well as a significant objective improvement in ECG ( $p < 0.05$ ) compared to controls.<sup>30</sup>

One of *Astragalus*’ saponins, *Astragaloside* IV, was isolated and injected into 19 patients with congestive heart failure, significantly improving left ventricular activity, end-systolic volume, and end-diastolic



volume ( $p < 0.05$ ). After two-weeks' treatment, 79 percent of patients had disappearance of chest pain and dyspnea.<sup>31</sup>

Administration of *Astragalus* in the above studies was via intravenous infusion. It is as yet unknown if oral intake of the root powder will result in similar efficacy.

## Discussion

This article highlights the cardiovascular effects of four potent traditional botanicals. Although these plants have been used in the treatment of heart disease for hundreds of years, current research methods show us they can be utilized effectively in deadly modern day diseases, including ischemic heart disease, congestive heart failure, arrhythmias, and hypertension. The unique flavonoids, OPCs, and saponins in these species provide their beneficial effects by improving the energy utilization and efficiency of the heart muscle. This improves the pumping action of the myocardium, ameliorating the symptoms of decreased myocardial function.

*Terminalia*, *Astragalus*, and *Inula*'s relief of anginal symptoms, and effect on ST-T-wave depression in ischemic heart disease is quite impressive, eliminating or improving this marker of ischemia in the majority of patients studied. This has the potential of improving the quality of life, while avoiding the side effects of conventional treatment.

*Crataegus*, *Astragalus*, and *Terminalia*'s efficacy in improving left ventricular function in congestive heart failure, which has an annual mortality rate of 40 percent using conventional treatment methods, should not be overlooked. The widespread use of these potent substances can improve the quality of life in individuals with heart disease, and potentially save thousands of lives.

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