Hawthorn

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Hawthorn, a common name of all plant species in the genus *Crataegus*, is a thorny shrub or small tree that normally has bright green leaves, white flowers, and bright red berries (Figure 1), each containing one to three or five seeds, depending on the species. Hawthorn is a member of the Rosaceae family and is recognized to have approximately 280 species primarily from northern temperate zones in East Asia, Europe, and eastern North America. It is a widely used herb for preventing and treating cardiovascular diseases.

At present, more than 20 species of hawthorn are used as herbal drugs or drug materials in the world. Some of them are officially listed in the pharmacopoeias of many countries such as China, Germany, France, and England (Table I).

**HISTORY AND TRADITIONAL USES**

Hawthorn has a long history of use in traditional Chinese medicine (TCM) and European herbal medicine. It was first mentioned for TCM in *Tang Ben Cao*, the world’s first official pharmacopoeia in 659 A.D. In Europe, the use of hawthorn can be dated back to the time of Dioscorides in the first century A.D. Its use for the treatment of heart disease began in the late 1800s.

In TCM, hawthorn fruits are used for stimulating digestion and promoting the function of the stomach, improving blood circulation, and removing blood stasis. Thus, they are used in prescriptions to treat indigestion with epigastric distension, diarrhea, and abdominal pain; amenorrhea; hypertension; and hyperlipidemia.

In Europe, hawthorn fruits, leaves, flowers, or a combination thereof have been traditionally used as an astringent, antispasmodic, cardiotonic, diuretic, hypotensive, and antiatherosclerotic agent. The herb is used to treat various heart problems, including heart failure, New York Heart Association (NYHA) stages I-II, angina pectoris, hypertension with myocardial insufficiency, mild alterations of cardiac rhythm, and atherosclerosis.

Both in China and Europe, hawthorn fruit is consumed not only for medicinal purposes mentioned above but also as foodstuff (e.g., canned fruit, jam, jelly, drink, and wine).

**CHEMICAL CONSTITUENTS**

Hawthorn fruits, leaves, and flowers contain a number of chemical constituents, such as flavonoids (0.1%-1% in fruits, 1%-2% in leaves and flowers), oligomeric proanthocyanidins (OPCs, 1%-3% in fruits or leaves with flowers), triterpene acids (0.5%-1.4% in fruits), organic acids (2%-6%), sterols, and trace amounts of cardioactive amines. Among these, flavonoids and OPCs are the two major groups of bioactive components. Many hawthorn preparations are standardized based on their flavonoid and OPC contents. Specific compounds and their structure, representative of the main chemical groups, are shown in Figures 2 to 5.
The main pharmacological activities are primarily cardiovascular. These include cardiotonic, antiarrhythmic, hypotensive, hypolipidemic, and antioxidative activities.

**Cardiotonic Activity**

Numerous in vitro and animal studies have tested the activities of water-soluble extract, flavonoid fraction, triterpene fraction, and OPC fraction, which are prepared from hawthorn fruits, leaves, or flowers as well as individual components of hawthorn (hyperoside, luteolin-7-glucoside, epicatechin, vitexin, and rutin). Marked cardiotonic actions have been observed: positive inotropic and negative chronotropic effect, increase of coronary blood flow and cardiac output, and reduction of oxygen consumption.\(^{16-20}\) These actions may be related to phosphodiesterase inhibitory effect.\(^{20,21}\)

**Antiarrhythmic Activity**

Hawthorn extracts from fruits or leaves with flowers have also been found to protect against heart arrhythmias induced by aconitine, calcium chloride, and chloroform-adrenaline in various in vitro and in vivo rat experiments.\(^{22-24}\)

**Hypotensive Activity**

When flavonoid, OPC, and triterpene acid extracts were administrated intravenously to various species of animals, prolonged dose-dependent hypotension in anaesthetized normotensive and hypertensive animals was observed.\(^{24-28}\) The hypotensive action was mainly attributed to peripheral vasodilation.\(^{29}\) In more recent studies, the hawthorn extract was found to induce endothelium-dependent relaxation in an isolated rat mesenteric artery.\(^{30}\) Procyanidins were identified as the major component for this effect.\(^{31}\)

**Hypolipidemic Activity**

Hawthorn has been found to decrease the serum levels of cholesterol, LDL-cholesterol, and triglyceride in hypercholesterolemic and atherosclerotic animals. It also significantly inhibits lipid deposition in the liver and aorta.\(^{32-35}\) When administered to rats fed with an atherogenic diet, the hawthorn fruit extract increased excretion of bile acid, depressed hepatic cholesterol synthesis, and significantly increased the binding of \(^{125}\)I-LDL to the liver plasma membranes, indicating an enhancement of the LDL-receptor activity.\(^{36}\)

**Antioxidative Activity**

In some in vitro studies, various hawthorn extracts from fruits, leaves, or flowers possess antioxidative activity.\(^ {9,37}\) These activities are likely to be related to OPCs and flavonoids, as individual OPCs and flavonoids, such as epicatechin, rutin, hyperoside, and isoquercitrin, have shown a strong inhibitory effect against human LDL oxidation.\(^ {38}\)

In various in vivo studies, an alcoholic extract has been found to produce a protective effect on oxidative stress in experimental atherosclerotic rats.\(^ {32}\) The extract prevented the increase of lipid peroxidation and

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Figure 1. Photographs of a hawthorn tree (Crataegus pinnatifida Bge. var. major N.E. Br.) (upper and left lower) and the Chinese medicine Shan Zha (right lower). Extracted from Zhonghua Renming Gonghegou Yaodian, Zhongyao Caise Tuji, 1995.
the decrease of glutathione and alpha-tocopherol content in the liver, aorta, and heart tissues. It also normalized the levels of antioxidant enzymes in the liver, aorta, and heart tissue\textsuperscript{32} and increased the activity of superoxide dismutase (SOD) in hyperlipidemic rats\textsuperscript{39} or mice.\textsuperscript{40}

**Pharmacokinetics**

So far, no pharmacokinetic study has been reported with any hawthorn active components after consumption of the hawthorn herb or its preparations.

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**Table I** Some Species of Hawthorn Officially Used as Herbal Drug or Drug Materials Worldwide

<table>
<thead>
<tr>
<th>Pharmacopoeias</th>
<th>Species Accepted</th>
<th>Parts Used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C. pinnatifida Bge. var. major N.E. Br.</td>
<td></td>
</tr>
<tr>
<td>German Pharmacopoeia (DAB, 1997) and Swiss Pharmacopoeia (1997)</td>
<td>C. oxyacantha L.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. monogyna Jacq.</td>
<td>Fruits, leaves, and flowers</td>
</tr>
<tr>
<td></td>
<td>C. pentagyna Waldst.</td>
<td></td>
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<tr>
<td></td>
<td>C. nigra Waldst.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. azarolus L.</td>
<td></td>
</tr>
<tr>
<td>France Pharmacopoeia (1998)</td>
<td>C. oxyacantha L.</td>
<td>Leaves with flowers</td>
</tr>
<tr>
<td></td>
<td>C. monogyna Jacq.</td>
<td></td>
</tr>
</tbody>
</table>

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Figure 2. The chemical structures of representative flavonoids in hawthorn.

Figure 3. The chemical structures of representative proanthocyanidins in hawthorn.

Figure 4. The chemical structures of representative triterpene acids in hawthorn.

Figure 5. The chemical structures of representative organic acids in hawthorn.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Jadad Scorea</th>
<th>Number of Patients</th>
<th>Plant Parts Used</th>
<th>Dosage</th>
<th>Duration (weeks)</th>
<th>Assessment Methods</th>
<th>Results (for hawthorn group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>Randomized, placebo controlled, double blind</td>
<td>3</td>
<td>136</td>
<td>Leaves with flowers</td>
<td>One capsule (80 mg extract [5:1, 18.75% OPCs]), bid</td>
<td>8</td>
<td>Bicycle ergometry exercise</td>
<td>A significant advantage in postexercise pressure/heart rate product, heart rate, and subjective patient symptomatology.</td>
</tr>
<tr>
<td>34</td>
<td>Open trial</td>
<td>0</td>
<td>30</td>
<td>Hyperlipidemia</td>
<td>250 ml drink (0.56 mg flavones per 100 ml) bid</td>
<td>4.3</td>
<td>Serum lipid analysis</td>
<td>Significantly decreased serum cholesterol (p &lt; 0.001), LDL-C, and triglyceride compared with that before treatment. Significant malondialdehyde reduction showed strong antioxidative effect.</td>
</tr>
<tr>
<td>42</td>
<td>Randomized, placebo controlled, double blind</td>
<td>5</td>
<td>85</td>
<td>Leaves with flowers</td>
<td>300 mg extract (3:1, 2.2% flavonoids) daily</td>
<td>4</td>
<td>Bicycle ergometry exercise</td>
<td>Exercise tolerance, pressure/heart rate product, and clinical symptomatology all showed a trend toward superiority but were not statistically significant.</td>
</tr>
<tr>
<td>43</td>
<td>Randomized, placebo controlled, double blind</td>
<td>4</td>
<td>78</td>
<td>Leaves with flowers</td>
<td>200 mg extract (3:1, 2.2% flavonoids) tid</td>
<td>8</td>
<td>Bicycle ergometry exercise</td>
<td>Statistically significant improvements in working capacity, systolic blood pressure, and heart rate during exercise. No effect on diastolic blood pressure.</td>
</tr>
<tr>
<td>44</td>
<td>Randomized, placebo controlled, double blind</td>
<td>5</td>
<td>132</td>
<td>Leaves with flowers</td>
<td>300 mg extract (3:1, 2.2% flavonoids) tid</td>
<td>8</td>
<td>Bicycle ergometry exercise</td>
<td>Effective in decreasing heart rate and in improving exercise tolerance and pressure/heart rate product. The severity of symptoms dropped by 50%. No effect on blood pressure.</td>
</tr>
<tr>
<td>45</td>
<td>Placebo controlled, double blind</td>
<td>1</td>
<td>30</td>
<td>Leaves with flowers</td>
<td>One capsule (80 mg extract [5:1, 18.75% OPCs]), bid</td>
<td>8</td>
<td>Bicycle ergometry exercise</td>
<td>Significant advantage in increase of heart work capacity, reduction of heart rate, improvement in pressure/heart rate product, and mild reduction of systolic and diastolic blood pressures.</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>40</td>
<td>NYHA stage II heart failure</td>
<td>Extract of hawthorn and passion-flower</td>
<td>6</td>
<td>Walking and bicycle ergometric tests</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>46</td>
<td>40</td>
<td></td>
<td>2 ml, tid</td>
<td></td>
<td>Slight but significant improved exercise capacity (about 10% above baseline), decrease in resting heart rate, diastolic blood pressure at rest, and total serum cholesterol and low-density lipids.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo controlled, double blind</td>
<td>4</td>
<td>NYHA stage II heart failure</td>
<td>Extract of hawthorn and passion-flower</td>
<td>6</td>
<td>Walking and bicycle ergometric tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Placebo controlled, double blind</td>
<td>2</td>
<td>Angina pectoris</td>
<td>Fruits</td>
<td>300 mg extract daily</td>
<td></td>
<td>A significant improvement was observed in the hawthorn group, with 84.8% of the antianginal effective rate and 46.4% of the ECG effective rate.</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Randomized, placebo controlled, double blind</td>
<td>4</td>
<td>Angina pectoris (NYHA stages I and II heart failure)</td>
<td>Leaves with flowers</td>
<td>60 mg extract (5:1, 18.75% OPCs) tid</td>
<td>3</td>
<td>Bicycle ergometry exercise</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Randomized, placebo controlled, double blind</td>
<td>5</td>
<td>NYHA stage II heart failure</td>
<td>Leaves and fruits</td>
<td>180 mg extract (5:1, 18.75% OPCs) daily</td>
<td>6</td>
<td>Bicycle ergometry exercise</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Randomized, placebo controlled, double blind</td>
<td>5</td>
<td>NYHA stage II heart failure</td>
<td>Leaves and fruits</td>
<td>180 mg extract (5:1, 18.75% OPCs) daily</td>
<td>6</td>
<td>Bicycle ergometry exercise</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>Randomized, placebo controlled, double blind</td>
<td>5</td>
<td>NYHA stage II heart failure</td>
<td>Extract of hawthorn and passion-flower</td>
<td>6</td>
<td>Walking and bicycle ergometric tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>Placebo controlled, double blind</td>
<td>2</td>
<td>Angina pectoris</td>
<td>Fruits</td>
<td>300 mg extract daily</td>
<td></td>
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<td>4</td>
<td>Angina pectoris (NYHA stages I and II heart failure)</td>
<td>Leaves with flowers</td>
<td>60 mg extract (5:1, 18.75% OPCs) tid</td>
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<td></td>
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<td>5</td>
<td>NYHA stage II heart failure</td>
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<td>180 mg extract (5:1, 18.75% OPCs) daily</td>
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</tr>
<tr>
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<td>Randomized, placebo controlled, double blind</td>
<td>4</td>
<td>Angina pectoris (NYHA stages I and II heart failure)</td>
<td>Leaves with flowers</td>
<td>60 mg extract (5:1, 18.75% OPCs) tid</td>
<td>3</td>
<td>Bicycle ergometry exercise</td>
<td></td>
</tr>
<tr>
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<td>Randomized, placebo controlled, double blind</td>
<td>5</td>
<td>NYHA stage II heart failure</td>
<td>Leaves and fruits</td>
<td>180 mg extract (5:1, 18.75% OPCs) daily</td>
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<td>Bicycle ergometry exercise</td>
<td></td>
</tr>
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<td>Randomized, placebo controlled, double blind</td>
<td>5</td>
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<td></td>
</tr>
</tbody>
</table>
CLINICAL STUDIES

Hawthorn preparations are potentially useful for early stages of congestive heart failure, hypertension, angina, and minor arrhythmia. This has been demonstrated in many clinical studies (see Table II).41-49 These results showed that hawthorn was effective in decreasing heart rate, improving exercise tolerance and pressure/heart rate product, and lowering serum lipids in patients with NYHA stage II heart failure or with hyperlipidemia. But in some of these studies, no effect on diastolic blood pressure was observed.43,44 Although serum lipids in the patients with hyperlipidemia were reduced by hawthorn in one clinical trial,34 the study was not controlled. Thus, the clinical benefit of this effect requires further confirmation.

DOSAGES

Hawthorn is a slow-acting herb and should be used for at least 4 to 8 weeks for full benefit. The dosage depends on the type of preparation and source material. Doses tested in European clinical studies ranged from 160 mg to 900 mg a day of hawthorn extract, which is standardized to contain 2.2% of flavonoids or 18.75% of oligomeric proanthocyanidins. Most commonly used dosage forms and dosage are the following:

In Europe:
- Standardized extract: 120 to 240 mg, three times a day51
- Tincture (1:5): 2 to 4 ml, three times a day51
- Tea: 1 to 2 teaspoons of fruits soaked for 15 minutes in 1 cup of water51

In China:
- 9 to 12 g of dried fruit, two or three times a day, used in hawthorn prescriptions or its products such as extract, tincture, or pill8

SIDE EFFECTS, TOXICITY, AND DRUG INTERACTIONS

No significant adverse events have been reported in clinical trials.

The acute toxicity (LD50) is 18.5 ml/kg in mice and 33.8 ml/kg in rats by oral administration of a 10% alcoholic extract solution of hawthorn leaves and fruit52 and 1.56 g/kg of the flavonoids fraction in mice intravenously.53 LD50 of the proanthocyanidins fraction is 130 mg/kg by i.p. and 300 mg/kg by s.c. in mice.54

Hawthorn may have a potentiating effect on digitalis, beta-blockers, and other hypotensive drugs. Modification of the drug dosage may be required.55,56 This potential drug interaction may be related to the cardiotonic and hypotensive effects of hawthorn.

SUMMARY

Hawthorn (Crataegus species) has long been regarded as a digestive and cardiotonic in traditional Chinese medicine and European herbal practice. The main constituents of hawthorn are flavonoids, triterpene acids, proanthocyanidins, and organic acids. Various animal studies have suggested that hawthorn extracts exert a wide range of pharmacological properties, especially on the cardiovascular system, including cardiotonic, antiarrhythmic, hypotensive, hypolipidemic, and antioxidant activities. These beneficial effects are mainly attributed to its flavonoid and proanthocyanidin components. Numerous clinical studies have demonstrated that hawthorn preparations are very effective in early stages of congestive heart failure, hypertension, angina, and minor arrhythmia. Hawthorn is currently used widely by practitioners and individuals in various parts of the world for the treatment of heart failure, hypertension, atherosclerosis, angina pectoris, indigestion, and abdominal distention.

REFERENCES

42. Bodigheimer K, Chase D: Effectiveness of hawthorn extract at a dosage of 3 x 100 mg per day: multicentre double-blind trial with 85 NYHA stage II heart failure patients. Munchener Medizinische Wochenschrift 1994;136:57-S11.


