There are more than 100 species of hawthorn in North America, consisting of small trees and shrubs. However, only a few are used for medicinal purposes. These include Crataegus laevigata, C. oxyacantha, C. monogyna and, less often, C. pentagyna. The name Crataegus oxyacantha is from the Greek: kratos (hard), oxus (sharp) and akantha (thorn). Common names for hawthorns, which are members of the Rosaceae family, include may, mayblossom, quick, thorn, whitethorn, haw hazels, gazels, halves, hagthorn, and bread and cheese tree. C. oxyacantha or C. monogyna are usually multibranched 2–5 meter shrubby trees that can reach a height of up to 10 meters. They prefer the forest margin at lower and warmer areas. The leaves are alternated, stalked, divided into 3–5 lobes and grayish-green on the underside. The scented white flowers grow in bunches and bloom from April to June, after which dark red, egg-shaped fruit develops. The flowering tops are collected in late spring and early summer. Berry-collecting starts in September and ends by late October.

Traditionally, the berries are used for their astringent properties in heavy menstrual bleeding and in diarrhea. The leaves also have been used as a substitute for green tea and in making liqueurs. Both the flowers and berries act as diuretics and can be used to treat kidney problems and dropsy. Recently, the flower has been widely used as a heart tonic. While research suggests that the flower contains more cardioactive components than do the berries, total extracts of both have been recommended to treat cardiac failure, arteriosclerosis, hypertension, angina pectoris, and a variety of geriatric conditions.

Chinese medicine employs the berries of C. pinnatifida as a digestive and circulatory stimulant.

CHEMICAL COMPOSITION AND PHARMACOLOGY

Flowers and leaves contain mixtures of chlorogenic acid and flavonoids such as quercin, hyperoside (quercetin 3-galactoside), vitexin and vitexin 4'-rhamnoside. Chlorogenic acid and caffeic acid have some analgesic effects. Quercetin has multiple actions: antiarrhythmic, antihepatotoxic and inhibitor of cAMP-phosphodies. Other flavonoids identified in Crataegus species are luteolin, luteolin-3',7 diglucosides, apigenin, apegemin-7-O-glucoside and rutin. Luteolin is an effective smooth muscle relaxant and protects the heart lipids against doxorubicin-induced lipid peroxidation. In addition, luteolin 5-rutinoside has achieved a marked antidiabetic activity in streptozocin-induced diabetes. Apigenin and luteolin inhibit tumor formation. Luteolin decreases aromatase enzyme activity; apigenin showed inhibitory effect on TPA-mediated tumor promotion and is antimutagenic.

Hawthorn contains amygdalin; it has been tested in cancer, but provided no substantive benefits. In fact, several patients experienced symptoms of cyanide toxicity with amygdalin therapy. The other major constituents are triterpenoids, e.g., oleanolic acid, ursolic acid and crataegus acid. Ursolic acid induced apoptosis in human leukemia cells, perhaps triggered by enhanced intracellular Ca²⁺ levels. Lowering Ca²⁺ levels inhibited the apoptotic action of ursolic acid. The antiproliferative action of ursolic acid was also indicated in a mouse melanoma cell line. Oleanolic acid and ursolic acid also have anti-inflammatory and antihyperlipidemic properties. Oleanolic acid is marketed in China as an oral drug for human liver disorders.

THERAPEUTIC ACTIONS

Cardiac Activity: Hawthorn extracts prepared from leaves and flowers were investigated for their effects on contraction, energy turnover, and the apparent refractory period in isolated cardiac myocytes from an adult rat heart. The hawthorn extract exhibited a positive inotropic effect accompanied by a moderate increase of oxygen consumption. This research compared the hawthorn extract with other known positive inotropic drugs, such as the beta-adrenergic agonist isoprenaline or the cardiac glycoside ouabain (gamma-strophantin); the effects of the hawthorn extract were significantly more economical with respect to the energy of the myocytes. Furthermore, the extract prolonged the apparent refractory period in the presence and absence of isoprenaline, which was indicative of an antiarrhythmic action as well.

Guinea pig hearts also were used to compare the influence of Crataegus extract to that of other inotropic drugs.
such as epinephrine, milrinon and digoxin. Different functional parameters were measured, focusing on the effective refractory period of the myocardium. Several cardiac parameters were measured to test the effect of the extract on the refractory period. All of the drugs except the Crataegus extract shortened the effective refractory period in a concentration-dependent manner. However, the Crataegus extract prolonged the effective refractory period by a maximum of 10%.

The main flavonoids of Crataegus species were tested on isolated guinea pig heart. O-glycosides, luteolin-7-glucoside, hyperoside and rutin increased the coronary flow (186%, 66%, and 66%, respectively) and the relaxation velocity. A slight, positive inotropic effect and a rise in the heart rate were also seen. The C-glycosides—vitexin, vitexin-rhamnoside and monoaetetyl-vitexin-rhamnoside—had similar, but less dramatic, effects. A possible beta-adrenergic effect of the glycosides was eliminated by propranolol treatment. Also, reserpine did not influence the myocardial action of hyperoside. These results and former experiments showed that an inhibition of 3', 5'-cAMP phosphodiesterase may be underlying the possible mechanism of the glycosides of the species.

Lactate dehydrogenase (LDH) is released from damaged heart cells and is used as a marker of myocardial injury following myocardial infarction. Rats were treated for three months with C. oxyacantha. When the coronary effluent was sampled for LDH content, the Crataegus group showed significantly lower LDH activity after reperfusion, indicating a preservation effect on the plasma membrane and protection from myocardial damage.

The effects of garlic (Allium sativum) and Crataegus were examined on isoprenaline-induced heart, liver and pancreas damage in rats. Hawthorn extract in combination with garlic powder showed protective effects in a dose-dependent manner. Clinical signs, histological and histoenzymatical findings, and determination of activities of succinate dehydrogenase (SDH), NADH-NBT reductase, acid phosphatase and glucose-6-phosphate dehydrogenase (G-6-DPH) were evaluated. Heart, hepatic and pancreatic tissue pretreated with 0.5 g/kg Allium sativum and 0.3 g/kg Crataegus showed a marked protective effect against tissue necrosis. Evaluation of hepatic and heart SDH in isoprenaline-treated animals given the drug combination mentioned above yielded significant enhancement of enzyme activity. In evaluating the other key enzyme activity G-6-DPH, the composition of 0.5 g/kg garlic and 0.3 g/kg Crataegus had a significant protective effect against necrosis induced by isoprenaline. The G-6-DPH activity increase was more pronounced in the heart, providing excellent protection against isoprenaline-induced myocardial lesions.

In a multicenter trial of 80 patients with heart problems originating from ischemia or hypertension, the group taking the hawthorn extract showed statistically significant (p < 0.01) improvement in cardiac function, palpitations, cardiac edema and shortness of breath. However, ECG results did not improve for the treated or placebo group.

IN A STUDY UTILIZING HAWTHORN AND OTHER HERBS, 87% OF TREATED SUBJECTS HAD LOWER TOTAL SERUM CHOLESTEROL

Another placebo-controlled, double-blind study involved 30 patients aged 50 to 70 years, who had New York Heart Association classification stage II cardiac insufficiency. Subjects were treated with either 80 mg dry extract or placebo twice a day for 8 weeks. Physical parameters tested patients’ performances on a standardized bicycle exercise program and evaluated responses to a questionnaire regarding patients’ assessments of their conditions. The active substance group showed a statistically significant improvement (p < 0.05) over the placebo group. No adverse effects were observed.

The efficacy of 60 mg of standardized Crataegus extract was tested in a double-blind, placebo-controlled, clinical study involving 36 multimorbid elderly patients (62–84 years of age) suffering from decreasing cardiac performance. Hemodynamic data were measured before and after exercise, and the patients’ subjective well-being was assessed. The pressure heart rate product (a measure of cardiac stress) significantly decreased under the active substance both in exercise and recovery phase; the blood pressure and heart rate also dropped. Fewer prematurely terminated exercise sessions also indicated the patients’ well-being, including psychological parameters.

In a meta-analysis of eight clinical studies evaluating heart failure, Crataegus extract improved both objective and subjective symptoms. The researchers concluded that hawthorn is safe and an effective therapeutic alternative for the treatment of heart failure.

Hypotensive Action: A water-alcoholic extract of a procyanidin isolated from C. oxyacantha has been tested on cats. An injected dosage of 3 mg/kg lowered the blood pressure of the cats from 160 to 110 mmHg. Stepka and Winters investigated 39 known Crataegus species and found 15 with mild to significant hypotensive activity.

Myocardial blood flow and arterial blood pressure were tested on nonanesthetized dogs and anesthetized cats. Oral administration of Crataegus (12–70 mg/kg) in the dogs and an injection of 15–35 mg/kg in the cats led to a significant increase in blood flow for several hours depending on the dose. A maximum 70% increase over resting flow was reached in the dogs. In cats, a similar result was associated with a slight decrease in arterial blood pressure.

Hypolipidemic Action: An alcoholic extract prepared from the berries of C. oxyacantha was tested on hyperlipidemic rats, and a significant decrease in lipid deposits in liver and aorta was observed. The reductions of cholesterol and triglycerides were progressive in the low density (LDL) and very low-density (VLDL) lipoprotein fractions. Further study revealed that the drug lowered the level of the atherogenic component, beta-lipoprotein. A similar study in rats fed an atherogenic diet showed that Crataegus tincture increased the LDL receptor-binding capacity in the liver and enhanced bile acid secretion. These observations indicated that Craetegus possibly up-regulates cholesterol influx into
the liver and enhances cholesterol degradation to bile acid while suppressing cholesterol biosynthesis. A Chinese clinical trial conducted on 130 hyperlipidemic subjects also achieved an impressive result with a combination of Chinese herbs, including C. pinnatifida. After the treatment, 87% of subjects had lower total serum cholesterol, and 80.8% also had lower triglyceride level.

Antioxidant Activity: While oxidation is part of a normal biological reaction, overloading the cells with free radicals could initiate the pathogenesis of many diseases. Some Crataegus constituents are predicted to be good antioxidants. The flower and fruit constituents responsible for free radical scavenging activity are epicatechin, hyperoside and chlorogenic acid. They are also among the best antilipoperoxidants. Phenolic compounds of Crataegus also have antioxidant activity. The flowers contain the most phenolic compounds, and the antioxidant activity of these extracts was clearly related to the phenolic contents.

Research supports the suggestion that Crataegus extracts used therapeutically for cardiovascular diseases should be standardized for oligomeric procyanidins (OPC) content. Anti-inflammatory Action: Recent research showed that macrophage-derived mediators—cytokines, interleukin-1 (IL-1) and tumor necrosis factor (TNF)—play a crucial role in inflammatory and immune responses. Therefore, inhibition of IL-1 and TNF could be criteria of anti-inflammatory activity. Extracts of the root of C. tanacetifolia showed inhibitory effect depending upon the concentration applied on IL-1 alpha and beta, and TNF alpha.

A hydroalcoholic extract from the flower heads of C. oxyacantha has inhibited thromboxane A2 biosynthesis in vitro. Further analysis showed that the following ingredients may be responsible for the action: vitexin, vitexin-2’-O-rhamnoside, quercetin and hyperoside from the flavonoid class. Also, significant inhibitions were observed with catechin and epicatechin from the flavonoid class.

A triterpene fraction isolated from C.-monogyna, which contained mainly cycloartenol, was tested against paw edema in rats. A 40 mg/kg oral dose had significant inhibition (61.5%) after 3 hours of administration. A similar action was observed in mice, measured with an inflammation test of the peritoneum. The triterpene fraction given orally to mice (40 mg/kg) inhibited peritoneal leukocyte infiltration by 89.4%. The fraction also showed weak inhibition of phospholipase A2 in vitro.

CNS Actions: The alcoholic extract of C. oxyacantha has shown direct influence on the CNS, having sedative, hypothermic and hypotensive actions. However, drug interactions are likely with other cardiovascular agents, generating unwanted synergetic effects. Hawthorn can potentiate cardiac glycoside action of digitalis (or other related drugs, such as digitoxin, digoxin, or gitalin). Patients who take these drugs should consult with a medical professional before taking hawthorn.

The recommended daily dosage is 0.3–1 g, or by infusion 2 teaspoons full three times daily, liquid extract 0.5–1.0 mL three times daily (1:1 in 25% alcohol) or tincture 1–2 mL three times daily (1:5 in 45% alcohol). Tincture combinations are available, such as hawthorn-cactus-motherwort-ginger, 15–30–40 drops, given three times daily. Hawthorn and its extracts can take up to two weeks to produce effects. For maximum benefit, they must be taken for at least 4–8 weeks.

CONCLUSION

The German Commission E made a positive recommendation about the flower and leaf extract of hawthorn. The combined pharmacological effects are positively inotropic, chronotropic and dromotropic. Its negative bathmotropic effect makes this herb unique among anti-arrhythmic drugs, with few adverse effects. The herb enhances coronary and myocardial circulation by dilating coronary vessels, relieving cardiac hypoxemia. Additional benefits are its hypotensive and hypolipidemic effects. In Europe, Crataegus extract gained full recognition in the treatment of age-related degenerative heart diseases. References available upon request to MSP.