International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.1, pp 458-465, Jan-Mar 2012

# *Crataegus oxyacantha* Linn. commonly known as Hawthorn-A Scientific Review.

**Lakshmi.T.[1]*, Geetha R.V.[2], Anitha Roy[1]**

**Faculty of Pharmacology, Saveetha Dental College and Hospitals, Chennai-77,India.**
**Faculty of Microbiology, Saveetha Dental College and Hospitals, Chennai-77,India.**

***Corres.Author: lakshmi085@gmail.com***

**Abstract:** Nature has been a source of medicinal agents for thousands of years and an impressive number of modern drugs has been isolated from natural sources, many based on their use in traditional medicine.Plant extracts are attractive sources of new drugs and have been shown to produce promising results in the treatment of various diseases.***Crataegus oxyacantha*** Linn., commonly known as Hawthorn, is one of the most widely used herbal plant with diverse pharmacological actions.It possess antioxidant and collagen stabilizing action. Hawthorn is used to treat a wide variety of inflammatory conditions, but primary use is treat hypertension, ischemic heart disease, congestive heart failure and arrhythmia. The chemical composition of Hawthorn includes vitamin C, Flavonoids, Glycosides, Saponins and Tannins,Cratategen, cardiotonic amines, Amygdalin ,pectins etc., Hence the aim of the present article is to compile all the data related to pharmacological aspects of this herbal plant .
**Key words**: ***Crataegus oxyacantha***, anti-inflammatory, anti-oxidant, Pharmacological activity, Amygdalin.

## Introduction:

***Crataegus oxyacantha,*** commonly known as Hawthorn (Family Rosaceae) is a thorny tree that thrives in hedgerows and fields in the temperate regions of Europe and the British Isles. Its name originates from the Greek word kratos meaning strength and refers to the nature of the wood. Other names include white thorn and hog berry. It blooms in May producing luscious red fruits and hence receives one of its most popular names, May-blossom [1]. Hawthorn tea is most widely known for its medicinal uses and primarily for its cardiovascular applications. Hawthorn is rich in triterpenic acids like oleanolic acid and ursolic acid ; polyphenols like, epicatechin, procyanidin B2, procyanidin B5, procyanidin C1, hyperoside, isoquercitrin and chlorogenic acid. [2]. The herb hawthorn have flavonoid pigments and procyanidin pigments in its flowers, berries and leaves, which is said to lower blood pressure and cholesterol. [3]The flavonoid content ,ologomeric proanthocyanidin possess good cardiotonic property.The drug from flowers has anti-spasmodic, hypotensive, cardiotonic, diuretic and nervine-sedative properties. Hawthorn is most valuable remedy for cardiovascular system and considered to be one of the best cardiac tonic [4]. The oligomeric proantho-cyanidins has strong vitamin P activity which is largely responsible for the cardiovascular activities. Vitamin P (citrin bioflavonoids) regulate the permeability of blood capillaries and promotes capillary stability when administered with vitamin C.[5] It is also utilized for their astringent qualities for relief of discomfort of sore throats, diarrhea and dysentery. Antioxidants found in hawthorn may aid to prevent some of the damage from free radicals, especially when it comes to heart disease.The berries, leaves, and flowers of the hawthorn plant have been used for medicinal purposes. Most modern preparations use the leaves and flowers, which are believed to contain more of the flavonoids than the berries.[6]. Hawthorn berries possess good diuretic property._Hence in the present article the clinical indications and pharmacological actions of the plant were reviewed comprehensively with reference to the scientific literatures.

**Table 1: Scientific Classification of *Crataegus Oxyacantha*.**

| | |
|---|---|
| Kingdom | Plantae |
| Order | Rosales |
| Family | Rosaceae |
| Genus | *Crataegus* |
| Species<br>Binomial name | *C. oxyacantha*<br>***Crataegus Oxyacantha*** |

**Fig 1: *Hawthorn Berries.***

**Fig 2: *Crataegus oxyacantha***

**Common Names** [7]: hawthorn, English hawthorn, harthorne, haw, hawthorne

**Latin Names** [8]: *Crataegus laevigata* (also known as *Crataegus oxyacantha*),*Crataegus monogyna*

**Parts used**: Berries/fruits, leaves.

**Active constituents** [9]:
Hawthorn leaves, berries, and blossoms contain biologicaly active flavonoid compounds like anthocyanidins and proanthocyanidins (also known as bioflavones or procyanidins).
Flavonoids are responsible for the red to blue colors of the hawthorn berries. Crataegus extracts also contain

- Cardiotonic amines like phenylethlamine, tyramine, isobutylamine, and o-methoxyphenyl ethylamine.
- Choline and acetylcholine.
- Purine derivatives: adenosine, adenine, guanine and caffeic acid
- Amygdalin.
- Pectins.
- Triterpene acids like ursolic, oleonic and crategolic acids.

**Plant Description**: [10]
Hawthorn is a common thorny shrub in the rose family that grows up to 5 feet tall on hillsides and in sunny wooded areas throughout the world. Its flowers bloom in May. They grow in small white, red, or pink clusters. Small berries called haws sprout after the flowers. They are usually red when ripe, but they may also be black. Hawthorn leaves are shiny and grow in a variety of shapes and sizes.

**History**:
Hawthorn was regarded as a valuable heart remedy as far back as the middle Ages. It was considered sacred in early times and believed to furnish the Crown of Thorns. Legend reveals that during AD30-63 Joseph of Aramathea came to England and planted his hawthorn staff in Glastonbury soil. Thus came to known as Glastonbury Thorn; grew and blossomed at Christmas

and Easter as if in celebration of the Christian Year. The Celts used Hawthorn in May celebrations using it to dress maypoles and symbolic effigies, and associated it with fertility.

**Mode of action** [11, 12]:
Hawthorn berries improves the heart circulation, acting upon the heart by either stimulating or depressing its activity depending upon the need. It results in dilation of the coronary blood supply and the tendency to slow down or stabilize the contractility of the heart muscle hence, it is safe to use as a long-term treatment for a weak or failing heart, and has a beneficial effect on cardiac arrhythmias.

Hawthorn berries causes reduction in elevated blood levels of pyruvic and lactic acid, normalization of prolonged systole and prevention of ECG changes due to hypoxia. It is a valuable herb for a strong and healthy heart due to its powerful antioxidant, anti-inflammatory and lipid-lowering properties.

**Clinical indications**:
* Lowers blood pressure.
* Increase the effectiveness of the heart's pumping action.
* Strengthen the heart muscle.
* Slow the heartbeat.
* Dilate coronary arteries.
* Prevent heart disease, heart attack and stroke.
* Help those healing from heart surgery.
* Support the immune system.
* Increase longevity.

The German Commission E - a scientific body which determines the effectiveness of herbal medicines - recommends tea or tincture of hawthorn for:
* Cardiac insufficiency of stages I and II as per NYHA classification.
* Feelings of pressure and tightness in the cardiac region.
* The ageing heart not yet requiring digitalis.
* Mild bradyarrhythmia.
* Increasing coronary and myocardial circulation.

**Pharmacological actions**:
**Anti-Hypertensive activity** [13-16]:
In a study carried out by M. Pittler and colleagues [13], 632 patients with chronic heart failure were treated with hawthorn and results showed that the hawthorn extract "significantly increased maximal workload compared with placebo" and reduced blood pressure and heart rate. Another study by Asgary S *et.al* has shown decease in both systolic and diastolic blood pressure in 92 patients with hypertension who took Iranian hawthorn for three months[14].
The first randomised controlled trial by Walker, Ann F *et al* demonstrated a hypotensive effect of hawthorn in patients with diabetes taking medication. Patients with type 2 diabetes (n = 79) were randomised to daily 1200 mg hawthorn extract
(n = 39) or placebo (n = 40) for 16 weeks and patients were assessed. At 16 week the patients who received hawthorn extract showerd statistically significant reduction of Diastolic blood pressure compared to placebo. [15]

An herbal drug containing D-camphor (CAS 76-22-2; 2.5 %) and a liquid extract of fresh hawthorn berries (97.3%), has been used since many years for the treatment of orthostatic hypotension. An epidemiological retrospective cohort study in 46 medical practices in Germany to investigate the efficacy and safety of drug. In his study patients were treated either with the test drug or a control drug containing etilefrine, oxilofrine, midodrine, norfenefrine or dihydroergotamine. A total of 490 patients (399 in the test-group and 91 in the control group) between 11 and 102 years were included in the study. To correct heterogeneities in baseline conditions, treatment results were adjusted by regression and stratification to equal baseline conditions using the propensity score. The adjusted odds ratio for improvement was 5.6, the adjusted mean increase of the systolic blood pressure the 2-fold compared to the control group.
The test drug was proven as effective and safe in the treatment of orthostatic hypotension in medical practice for all age groups and independent of the initial blood pressures. [16]

**Congestive Cardiac Failure**:
**Hwang *et al*** conducted a study on the effects of hawthorn treatment on remodeling and function of the left ventricle, after 1 month of pressure overload-induced cardiac hypertrophy. In his study Sprague-Dawley rats (male, 300 g) were subjected to sham operation or aortic constriction for 4 weeks and treated with Hawthorn (Crataegus-Extract- WS1442; 1.3, 13, 130 mg kg (-1) day (-1); AC-L, AC-M, AC-H) or vehicle (SH-V, AC-V) for 3 weeks after surgery. Systolic and diastolic function were measured using echocardiographic assessment at baseline and 4 weeks after AC. AC increased the LV/body weight ratio by 34% in vehicle and hawthorn treated rats.He concluded that Hawthorn treatment modifies left ventricular remodeling and counteracts myocardial dysfunction in early pressure overload-induced cardiac hypertrophy.[17]

**Degenring FH** conducted a randomised double blind placebo controlled clinical trial of *Crataegus oxyacantha* and *monogyna* in patients with congestive heart failure NYHA class II.A total of 143 patients (72 men, 71 women, mean age of 64.8 years were recruited and treated with 3 times 30 drops of the extract (n = 69) or placebo (n = 74) for 8 weeks. The primary variable for the evaluation of efficacy was the change in exercise tolerance determined with bicycle exercise testing, secondary variables included the blood pressure-heart rate product. The study showed significant improvement in recruited NYHA II patients with the standardised extract of fresh Crataegus berries. [18]

In a multicenter, placebo-controlled double-blind study, the efficacy of the Crataegus-Special extract (WS 1442) in patients with NYHA stage II cardiac insufficiency was investigated. A total of 136 patients with this diagnosis were admitted to the study and, following a 2-week run-in phase, treated with Crataegus-Special extract or placebo over a period of 8 weeks. The primary target parameter was the change in the difference of the pressure, heart rate product (systolic blood pressure x heart rate/100) (PHRP 50 W load vs. rest) measured at the beginning and end of treatment. On the basis of this variable, a clear improvement in the performance of the heart was shown in the group receiving the test substance, while the condition of the placebo group progressively worsened. The therapeutic difference between the groups was statistically significant. The results of the present clinical investigation confirm those of previous studies showing that Crataegus-Special extract WS 1442 is an effective and low-risk phytotherapeutic form of treatment in patients with NYHA II cardiac insufficiency. [19]

In 30 patients with stage NYHA II cardiac insufficiency, a placebo-controlled randomized double-blind study was carried out to determine the efficacy of the Crataegus special extract WS 1442. Treatment duration was 8 weeks, and the substance was administered at a dose of 1 capsule taken twice a day. The main target parameters were alteration in the pressure-x-rate product (PRP) under standardised loading on a bicycle ergometer, and a score of subjective improvement of complaints elicited by a questionnaire. Secondary parameters were exercise tolerance and the change in heart rate and arterial blood pressure. The active substance group showed a statistically significant advantage over placebo in terms of changes in PRP (at a load of 50 W) and the score, but also in the secondary parameter heart rate. In both groups, systolic and diastolic blood pressure was mildly reduced. [20]

**Immuno stimulant activity**:
Hawthorn extract may enhance immune system function, according to Phyllis Balch, author of "Prescription for Nutritional Healing." [21]The chemical compounds in hawthorn extract may encourage the production of white blood cells, which attack and destroy viruses, bacteria and fungi that can cause disease and illness.

**Sivasithambaram N Devaraj** [22] conducted a study on neuroprotective effect for Hawthorn (Crataegus oxyacantha) ethanolic extract in middle cerebral artery occlusion-(MCAO) induced stroke in rats. He focussed more on the immunomodulatory effect on male Sprague Dawley rats.In his study after 15 days of treatment with Hawthorn extract [100 mg/kg, pretreatment (oral)], male Sprague Dawley rats underwent transient MCAO for 75 mins followed by reperfusion (either 3 or 24 hrs). He measured pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), ICAM-1, IL-10 and pSTAT-3 expression in the brain by appropriate methods. He also looked at the cytotoxic T cell sub-population among leukocytes (FACS) and inflammatory cell activation and recruitment in brain (using a myeloperoxidase activity assay) after ischemia and reperfusion (I/R). Apoptosis (TUNEL), and Bcl-xL- and Foxp3- ($T_{reg}$ marker) positive cells in the ipsilateral hemisphere of the brain were analysed separately using immunofluorescence.

The results indicate that occlusion followed by 3 hrs of reperfusion increased pro-inflammatory cytokine and ICAM-1 gene expressions in the ipsilateral hemisphere, and that Hawthorn pre-treatment significantly ($p \leq 0.01$) lowered these levels. Furthermore, such pre-treatment was able to increase IL-10 levels and Foxp3-positive cells in brain after 24 hrs of reperfusion. The increase in cytotoxic T cell population in vehicle rats after 24 hrs of reperfusion was decreased by at least 40% with Hawthorn pretreatment. In addition, there was a decrease in inflammatory cell activation and infiltration in pretreated brain. Hawthorn pretreatment elevated pSTAT-3 levels in brain after I/R. They observed an increase in Bcl-xL-positive cells, which in turn might have influenced the reduction in TUNEL-positive cells compared to vehicle-treated brain.
In this study he concluded that, Hawthorn extract helped alleviate pro-inflammatory immune responses associated with I/R-induced injury, boosted IL-10 levels, and increased Foxp3-positive $T_{regs}$ in the brain, which may have aided in suppression of activated inflammatory cells. Such treatment also minimizes apoptotic cell death by influencing STAT-3 phosphorylation and Bcl-xL expression in the brain. Taken together, the immunomodulatory effect of

Hawthorn extract may play a critical role in the neuroprotection observed in this MCAO-induced stroke model.

**Anti Hyperlipidemic activity**:
During the last decades hawthorn has received much attention because of its potential to reduce plasma cholesterol and triacylglycerol (TAG) concentrations [23–32]

The summer green berries, flowers and young spring leaves of hawthorn contain the highest percentage of medicinal components, which include flavonoids such as quercetin, vitexin, and rutin, as well as oligomeric procyanidins (OPCs). Several studies have shown the therapeutic value of Hawthorne value in lowering blood cholesterol levels. OPCs stimulate the release of endothelial nitric oxide synthase (ENOS), an enzyme that increases the levels of nitric oxide (NO), which is a vasorelaxant and acts to decrease platelet aggregation and adhesion, as well as inhibiting the oxidation of LDL- cholesterol, all of which can protect against thermogenesis and thrombus formation. Use of hawthorn to reduce blood cholesterol, a 6:1 preparation is recommended, providing 2 g of concentrated solid extract of hawthorn in one-fourth teaspoon of water, juice or other liquid three times daily. Hawthorn may be standardized to 2% vitexin, 1.8% vitexin-4'-rhamnoside, and/or 20% procyanidins per dose. Other popular preparations include hawthorn capsules and tablets, which vary from 200 to 900 mg per dose [33]

**Yuguang Lin** [34] investigated the effect of hawthorn on cholesterol metabolism in hamsters and in human Caco-2 cells.in his study Hawthorn powder extracts inhibited acylCoA: cholesterol acyltransferase (ACAT) activity in Caco-2 cells. The inhibitory activity was positively associated with triterpenic acid (i.e., oleanolic acid (OA) and ursolic acid (UA)) contents in the extracts. Cholesterol lowering effects of hawthorn and its potential additive effect in combination with plant sterol esters (PSE) were further studied in hamsters. Animals were fed a semi-synthetic diet containing 0.08% (w/w) cholesterol (control) or the same diet supplemented with (i) 0.37% hawthorn dichloromethane extract, (ii) 0.24% PSE, (iii) hawthorn dichloromethane extract (0.37%) plus PSE (0.24%) or (iv) OA/UA mixture (0.01%) for 4 weeks. Compared to the control diet, hawthorn, PSE, hawthorn plus PSE and OA/UA significantly lowered plasma non-HDL (VLDL + LDL) cholesterol concentrations by 8%, 9%, 21% and 6% and decreased hepatic cholesterol ester content by 9%, 23%, 46% and 22%, respectively. The dichloromethane hawthorn extract lowered plasma non- HDL-C by 8% without changing HDL-C. This finding is further supported by the fact that the hawthorn extract also reduced hepatic total cholesterol and CE contents. Hepatic cholesterol esters are the storage form of cholesterol in the liver. In rodents such as mice and hamsters, hepatic CE concentration is more sensitive than plasma cholesterol in reflecting to the cholesterol lowering effect of dietary ingredients. Besides in hamsters, hawthorn extracts have been reported to lower plasma cholesterol concentration in rats and rabbits [23]. All these results provide scientific evidence, that hawthorn could be a useful natural ingredient for lowering plasma cholesterol concentrations in humans.Furthermore; his study proved that the combination of hawthorn extract with PSE had an additive cholesterol lowering effect.

**Antiinflammatory, Gastroprotective, free radical scavenging and antimicrobial activity**:
A study was carried out by **Vanja M tadic *et al*** [35] to test free-radical-scavenging, anti-inflammatory, gastro protective and antimicrobial activities of the ethanolic extract of hawthorn berries. Phenolic compounds represented 3.54%, expressed as gallic acid equivalents. Determination of total flavonoid aglycones content yielded 0.18%. The percentage of hyperoside, as the main flavonol component, was 0.14%. With respect to procyanidins content, the obtained value was 0.44%. DPPH radical-scavenging capacity of the extract was concentration-dependent, with EC50 value of 52.04 microg/mL. Oral administration of investigated extract caused dose-dependent anti-inflammatory effect in a model of carrageenan-induced rat paw edema. The obtained anti-inflammatory effect was 20.8, 23.0, and 36.3% for the extract doses of 50, 100, and 200 mg/kg, respectively. In comparison to indomethacin, given in a dose producing 50% reduction of rat paw edema, the extract given in the highest tested dose (200 mg/kg) showed 72.4% of its activity. Gastroprotective activity of the extract was investigated using an ethanol-induced acute stress ulcer in rats with ranitidine as a reference drug. Hawthorn extract produced dose-dependent gastroprotective activity (3.8 2.1, 1.9 1.7, and 0.7 0.5 for doses of 50, 100, and 200 mg/kg, respectively), with the efficacy comparable to that of the reference drug. Antimicrobial testing of the extract revealed its moderate bactericidal activity, especially against gram-positive bacteria *Micrococcus flavus, Bacillus subtilis, and Lysteria monocytogenes*, with no effect on *Candida albicans*.

**Safety**:
Hawthorn does not produce any side effects and drug interactions, hence is considered to be as a safer drug, for this reason it is recommended for long term use.

**Precautions and warning**:
There are no side effects, although preparations might intensify some herbal medications. Hence proper consultation with a herbalist or physician is required when hawthorn is to be taken for treatment of cardiovascular diseases and is contra indicated in pregnancy, breast feeding, infants and children.

## Discussion:

With herbal supplements gaining importance in recent therapeutic strategies, delineating the mechanisms of action for herbal supplements already used as therapies may increase their potential uses against different human pathologies. Hawthorn (***Crataegus monogyna*** Jacq. and ***Crataegus oxyacantha*** L.; sin. ***Crataegus laevigata*** (Poiret) DC.,Family-Rosaceae) leaves, flowers, and berries are used in traditional medicine in the treatment of chronic heart failure, angina pectoris, high blood pressure, arrhythmia and various digestive ailments as well as geriatric and antiarteriosclerosis remedies. The flowers and berries are rich in bioflavonoids and the leaves contain high levels of polyphenols, tannins and ologomeric proanthocyanidin (OPCs) which are 20 times more potent than Vitamin C and 50 times more potent than Vitamin E.

According to European Pharmacopoeia 6.0, hawthorn berries consist of the dried false fruits of Crataegus species or their mixture. Ologomeric proanthocyanidin possess good Cardiotonic activity. It is also useful in peripheral circulatory conditions, such as intermittent claudication and Raynaud`s disease. The flavonoids in hawthorn berries are vasodilatory, as is the condensed tannin phlobaphene. These dilate the peripheral blood vessels and have a specific action on the coronary circulation.

## Conclusion:

Since most of the work is done related to cardiovascular system and management of cholesterol, Antioxidant, Gastro protective(*in vivo*),Antimicrobial activity, henceforth we are aiming to focus on the role of hawthorn berries in the management of diarrhoea (*in vitro*) and to find out the active constituent responsible for the same.

**Acknowledgement:**
The authors are grateful to the authors/editors of all those articles, journals and books from where the literature for this article has been reviewed and discussed.
**Conflict of Interest**: Nil.

## References:

1. Weihmayr T, Ernst E, Therapeutic effectiveness of crataegus,fortschr med 1996;114:27-29.
2. T. Cui, J.-Z. Li, H. Kayahara, L. Ma, L.-X. Wu, and K. Nakamura, "Quantification of the polyphenols and triterpene acids in Chinese hawthorn fruit by high-performance liquid chromatography," *Journal of Agricultural and Food Chemistry*, vol. 54, no. 13, pp. 4574–4581, 2006.
3. Mills S bone K.priciples and practice of phytotherapy: modern herbal medicine Edinburg UK: Churchill Livingstone; 2000:439-447.
4. HAWTHORN (*CRATAEGUS OXYACANTHA*) INTERNATIONAL SCIENTIC AND CLINICAL STUDIES AVAILABLE AT http://wingsheartformula.com/research-information/hawthorne.
5. Vitamin P available at http://www.thefree dictionary.com/vitamin+p.
6. Blumenthal M, Goldberg A, Brinckmann J. Herbal Medicine: Expanded Commission E Monographs. Newton, MA: Integrative Medicine Communications; 2000:182-192.
7. Hawthorn. Natural Medicines Comprehensive Database Web site. Accessed at www.natural database.com on July 23, 2009.
8. Hawthorn in National centre for complementary and alternative medicine http://nccam.nih. gov/health/hawthorn/.
9. Amy, B., Deanna, M. and Christy, W. Hawthorn (online): 2006 (2006 October 10) Available at http//www.geocities.com/chadrx/hawth.html.
10. Hawthorn overview available at http://www.umm.edu/altmed/articles/hawthorn-000256.htm.
11. Hawthorn Berries available at http://www.spellbinderz.com/index.php?main_ page=product_info&products_id=153.
12. Hawthorn the Ultimate herb for your heart available at http://www.suite101.com/content/ hawthorn---the-ultimate-herb-for-your-heart-a339597.
13. Pittler MH, Schmidt K, Ernst E. "Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials." Am J Med 2003; 114(8):665-674.

14. Asgary S *et.al*, "Antihypertensive effect of Iranian Crataegus curvisepala Lind", Drugs Exp Clin Res. 2004; 30(5-6):221-5.

15. Walker, Ann F *et al*; Hypotensive effects of hawthorn for patients with diabetes taking prescription drugs: a randomised controlled trial. British Journal of General Practice, Volume 56, Number 527.

16. Hempel B, Kroll M, Schneider B. Robugen GmbH Pharmazeutische Fabrik, Esslingen-Zel; "Efficacy and safety of an herbal drug containing hawthorn berries and D-camphor in hypotension and orthostatic circulatory disorders/results of a retrospective epidemiologic cohort study". Arzneimittelforschung. 2005; 55(8):443-50. [Article in German]

17. Hwang HS, Bleske BE, Ghannam MM, Converso K, Russell MW, Hunter JC, Boluyt MO.Effects of hawthorn on cardiac remodeling and left ventricular dysfunction after 1 month of pressure overload-induced cardiac hypertrophy in rats. Cardiovasc Drugs Ther. 2008 Feb; 22(1):19-28.

18. Degenring FH, Suter A, Weber M, Saller R.Bioforce AG, Roggwil;A randomised double blind placebo controlled clinical trial of a standardised extract of fresh Crataegus berries (Crataegisan) in the treatment of patients with congestive heart failure NYHA II.Phytomedicine. 2003; 10(5):363-9.

19. Weikl A, Assmus KD, Neukum-Schmidt A, Schmitz J, Zapfe G, Noh HS, Siegrist J Crataegus Special Extract WS 1442. Assessment of objective effectiveness in patients with heart failure (NYHA II) Fortschr Med. 1996 Aug 30; 114(24):291-6.

20. Leuchtgens H;Crataegus Special Extract WS 1442 in NYHA II heart failure. A placebo controlled randomized double-blind study. Fortschr Med. 1993 Jul 20; 111(20-21):352-4.

21. Hawthorn Extract for Medical Uses available at http://www.livestrong.com/article/409766-hawthorn-extract-for-medical-uses

22. Chinnasamy Elango and Sivasithambaram N Devaraj* Immunomodulatory effect of Hawthorn extract in an experimental stroke modelJournal of Neuroinflammation 2010, 7:97.

23. Z. Zhang, W. K. K. Ho, YU. Huang, E. J. Anthony, L. W. Lam, and Z.-Y. Chen, "Hawthorn fruit is hypolipidemic in rabbits fed a high cholesterol diet," *Journal of Nutrition*, vol. 132, no. 1, pp. 5–10, 2002.

24. Z. Zhang, W. K. K. Ho, Y. Huang, and Z.-Y. Chen, "Hypocholesterolemic Activity of hawthorn fruit is mediated by regulation of cholesterol-7$\alpha$-hydroxylase and acyl CoA: cholesterol acyltransferase," *Food Research International*, vol. 35, no. 9, pp. 885–891, 2002.

25. S. Shanthi, K. Parasakthy, P. D. Deepalakshmi, and S. N. Devaraj, "Hypolipidemic activity of tincture of Crataegus in rats," *Indian Journal of Biochemistry and Biophysics*, vol. 31, no. 2, pp. 143–146, 1994.

26. S. Rajendran, P. D. Deepalakshmi, K. Parasakthy, H. Devaraj, and S. N. Devaraj, "Effect of tincture of Crataegus on the LDLreceptor activity of hepatic plasma membrane of rats fed an atherogenic diet," *Atherosclerosis*, vol. 123, no. 1-2, pp. 235– 241, 1996.

27. J. D. Chen, Y. Z. Wu, Z. L. Tao, Z. M. Chen, and X. P. Liu,"Hawthorn (shan zha) drink and its lowering effect on blood lipid levels in humans and rats,"*World Review of Nutrition and Dietetics*, vol. 77, pp. 147–154, 1995.

28. J. Chen, B. Xue, K. Li, J. Shi, D. Krempin, M. Zhu et al., "The effects of an instant haw beverage on lipid levels, antioxidant enzyme and immune function in hyperlipidemia patients," *Zhonghua Yu Fang Yi Xue Za Zhi*, vol. 36, pp. 172–175, 2002.

29. Y. Guan and S. Zhao, "Yishou jiangzhi (de-blood-lipid) tablets in the treatment of hyperlipemia," *Journal of Traditional Chinese Medicine*, vol. 15, no. 3, pp. 178–179, 1995.

30. Z.-Y. Chen, R. Jiao, and Y. M. Ka, "Cholesterol-lowering nutraceuticals and functional foods," *Journal of Agricultural and Food Chemistry*, vol. 56, no. 19, pp. 8761–8773, 2008.

31. Y. Lin, G.W.Meijer, M. A. Vermeer, and E. A. Trautwein, "Soy protein enhances the cholesterol-lowering effect of plant sterol esters in cholesterol-fed hamsters," *Journal of Nutrition*, vol. 134, no. 1, pp. 143–148, 2004.

32. T. Pl¨osch, J. K. Kruit, V. W. Bloks et al., "Reduction of cholesterol absorption by dietary plant sterols and stanols in mice is independent of the Abcg5/8 transporter," *Journal of Nutrition*, vol. 136, no. 8, pp. 2135–2140, 2006.

33. Ellen Kamhi Ph.D., R.N., and Eugene Zampieron, N.D., A.H.G. Managing Cholesterol Naturally April 2005 available at http://www.naturalnurse.com/cholesterol.htm.

34. Yuguang Lin,Mario A. Vermeer, and Elke A. Trautwein Triterpenic Acids Present in Hawthorn Lower Plasma Cholesterol by Inhibiting Intestinal ACAT Activity in Hamsters Evidence-Based Complementary and Alternative Medicine Volume 2011, Article ID 801272, 9 pages.

35. Vanja M Tadić, Silva Dobrić, Goran M Marković, Sofija M Dordević, Ivana A Arsić, Nebojsa R Menković, Tanja Stević Anti-inflammatory, gastroprotective, free-radical-scavenging, and antimicrobial activities of hawthorn berries ethanol extract. Journal of Agricultural and Food Chemistry (2008) Volume: 56, Issue: 17, Pages: 7700-7709.

*****