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## List of references supporting the assessment of *Crataegus spp.*, folium cum flore

Draft

**The Agency acknowledges that copies of the underlying works used to produce this monograph were provided for research only with exclusion of any commercial purpose.**

Amel B, Seddik K, Shtaywy A, Saliha D, Mussa AZ, Assia B, Saliha D, Abderahmane B, Smain A. Phytochemical analysis, antioxidant activity and hypotensive effect of algerian azarole (*Crataegus azarolus L.*) leaves extracts. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 2014, 5(2): 286-305

Ammon HPT, Hänel M. *Crataegus*, toxicology and pharmacology. Part III: Pharmacodynamics and pharmacokinetics. *Planta Medica* 1981, 43:313-322

Asher GN, Viera AJ, Weaver MA, Dominik R, Caughey M, Hinderliter AL. Effect of hawthorn standardized extract on flow mediated dilation in prehypertensive and mildly hypertensive adults: a randomized, controlled cross-over trial. *BMC complementary and alternative medicine* (2012), doi: 10.1186/1472-6882-12-26

Blaschek W, Hilgenfeldt U, Holzgrabe U, Reichling J, Ruth P, Schulz V. (editors) HagerROM 2011. Hagers Enzyklopädie der Arzneistoffe und Drogen. Version 10.3. Springer Medizin Verlag, Heidelberg 2011

Bleske BE1, Zineh I, Hwang HS, Welder GJ, Ghannam MM, Boluyt MO. Evaluation of hawthorn extract on immunomodulatory biomarkers in a pressure overload model of heart failure. *Medical Science Monitor: International Medical Journal of experimental and clinical Research* (2007), 13(12): 255-258

Bödigheimer K, Chase D. Wirksamkeit von Weißdorn-Extrakt in der Dosierung 3 mal 100 mg täglich. [Effectiveness of hawthorn extract at a dosage of 3 x 100 mg per day.] *Münchener medizinische Wochenschrift* 1994, 136(Suppl. 1):7-11

Bradley P. (editor) British Herbal Compendium – A handbook of scientific information on widely used plant drugs, Volume 2. British Herbal Medicine Association, Bournemouth; 2006

Brixius K, Frank K, Münch G, Müller-Ehmsen J, Schwinger RHG. WS 1442 (*Crataegus* Spezialextrakt) wirkt am insuffizienten menschlichen Myokard Kontraktionskraft-steigernd. *Herz Kreislauf* 1998, 30:28-33



Brixius K, Willms S, Napp A, Tossios P, Ladage D, Bloch W, Mehlhorn U, Schwinger RH. Crataegus special extract WS 1442 induces an endothelium-dependent, NO-mediated vasorelaxation via eNOS-phosphorylation at serine 1177. *Cardiovascular Drugs and Therapy* (2006), 20(3): 177-184

Bubik MF, Willer EA, Bihari P, Jürgenliemk G, Ammer H, Krombach F et al. A novel approach to prevent endothelial hyperpermeability: the Crataegus extract WS® 1442 targets the cAMP/Rap1 pathway. *Journal of Molecular and Cellular Cardiology* (2012), 52(1): 196-205

Chang Q, Zuo Z, Ho WK, Chow MS. Comparison of the pharmacokinetics of hawthorn phenolics in extract versus individual pure compound. *Journal of Clinical Pharmacology* (2005a), 45(1): 106-112

Chang Q, Zuo Z, Harrison F, Chow MS. Hawthorn. *Journal of Clinical Pharmacology* 2002, 42(6): 605-612

Chang WT, Dao J, Shao ZH. Hawthorn: Potential roles in cardiovascular disease. *The American Journal of Chinese Medicine* (2005b), 33(1): 1-10

Commission E (Germany) monograph. *Crataegus*. *Bundesanzeiger* Nr. 1, 03 January 1984

Commission E (Germany) monograph. *Crataegi folium cum flore*. *Bundesanzeiger* Nr. 133, 19 July 1994

Commission E (Germany) monograph. *Crataegi folium*. *Bundesanzeiger* Nr. 133, 19 July 1994

Commission E (Germany) monograph. *Crataegi flos*. *Bundesanzeiger* Nr. 133, 19 July 1994

Daniele C, Mazzanti G, Pittler MH, Ernst E. Adverse event profile of *Crataegus spp.*: A systematic review. *Drug Safety* 2006, 29(6):523-535

Dalli E, Colomer E, Tormos MC, Cosín-Sales J, Milara J, Esteban E, Sáez G. Crataegus laevigata decreases neutrophil elastase and has hypolipidemic effect: a randomized, double-blind, placebo-controlled trial. *Phytomedicine* 2011, 18(8-9): 769-775

Dalli E, Vallés J, Cosín-Sales J, Santos MT, Moscardó A, Milara J, Sotillo JF. Effects of hawthorn (*Crataegus laevigata*) on platelet aggregation in healthy volunteers. *Thrombosis Research* 2011b, 128(4): 398-400

Dasgupta A, Kidd L, Poindexter BJ, Bick RJ. Interference of hawthorn on serum digoxin measurements by immunoassays and pharmacodynamic interaction with digoxin. *Archives of pathology & laboratory medicine* 2010, 134:1188-1192

Dood KP, Frey AD, Geisbuhler TP. The effect of Hawthorn extract on the coronary flow. *Journal of Evidence-Based Complementary & Alternative Medicine* (2013), 18(4): 257-267

Edwards JE, Brown PN, Talent N, Dickinson TA, Shipley PR. A review of the chemistry of the genus *Crataegus*. *Phytochemistry* 2012, 79: 5-26

Eggeling T, Regitz-Zagrosek V, Zimmermann A, Burkart M. Baseline severity but not gender modulates quantified *Crataegus* extract effects in early heart failure - A pooled analysis of clinical trials. *Phytomedicine* 2011, 18:1214-1219

Eichstädt H, Bäder M, Danne O, Kaiser W, Stein U, Felix R. *Crataegus*-Extrakt hilft dem Patienten mit NYHA II-Herzinsuffizienz. *Therapiewoche* 1989, 39:3288-3296

Ernst E. Possible interactions between synthetic and herbal medicinal products. Part 1: a systematic review of the indirect evidence. *Perfusion* 2000a, 13:4-15

Ernst SM. Herb-Drug Interaction Handbook. 1<sup>st</sup> edition. Church Street Books, Nassau NY 2000b, 109-111

ESC. Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal 2012, 33: 1787-1847

European Pharmacopoeia 8<sup>th</sup> Edition 2014 (2014a) (8.1); Ref. 01/2010:1432)

European Pharmacopoeia 8<sup>th</sup> Edition 2014 (2014b) (8.1); Ref. 01/2008:1864

European Pharmacopoeia 8<sup>th</sup> Edition 2014 (2014c) (8.1); Ref. 01/2010:1865)

Förster A, Förster K, Bühring M, Wolfstädter HD. *Crataegus* bei mäßig reduzierter linksv ventrikulärer Auswurffraktion. [Crataegus for moderately reduced left ventricular ejection fraction.] *Münchener medizinische Wochenschrift* 1994, 136(Suppl. 1):21-26

Frerichs G, Arends G, Zörnig H. (editors) Hagers Handbuch der pharmazeutischen Praxis. Vol. 1. Verlag von Julius Springer, Berlin 1925, 1111

Frishman WH, Grattan JG, Mamani R. Alternative and complementary medical approaches in the prevention and treatment of cardiovascular disease. Current problems in cardiology 2005, 30(8): 383-459

Fürst R, Zirrgiebel U, Totzke F, Zahler S, Vollmar AM, Koch E. The Crataegus extract WS 1442 inhibits balloon catheter-induced intimal hyperplasia in the rat carotid artery by directly influencing PDGFR-beta. *Journal of Atherosclerosis Research* (2010), 211(2): 409-417

Gehes Codex. Codex der pharmazeutischen Spezialpräparate mit Angaben über Zusammensetzung, Indikationen, Zubereitungsformen und Herstellern. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1953, 386

German Standard Marketing Authorisation: Weißdornblätter mit Blüten Nr. 1349.99.99 published 04/1986

Gruenwald J, Brendler T, Jaenicke C. PDR for herbal medicines. 4<sup>th</sup> ed. Thomson Healthcare Inc., Montvale 2007, 279-284

Guo R, Pttler MH, Ernst E. Hawthorn extract for treating chronic heart failure (review). Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No. CD005312. DOI: 10.1002/14651858.CD005312.pub2

HagerRom 2013 Hagers Enzyklopädie der Arzneistoffe und Drogen. Wissenschaftliche Verlagsgesellschaft mbH Stuttgart

Hartke K, Mutschler E. Deutsches Arzneibuch (DAB) 9 Kommentar: DAB, 9. Ausgabe. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1988, 3515-3520

Hecker-Niediek AE. Untersuchungen zur Biogenese, Markierung und Pharmakokinetik der Procyanidine aus *Crataegus*-Spezies [Dissertation]. Marburg: Marburg Univ., 1983

Holubarsch CJ, Colucci WS, Meinertz T, Gaus W, Tendera M. The efficacy and safety of *Crataegus* extract WS 1442 in patients with heart failure: The SPICE trial. *European Journal of Heart Failure* 2008, 10:1255-1263

Hoppe HA. Drogenkunde. Vol. 1. 8<sup>th</sup> ed. Walter de Gruyter, Berlin – New York 1975, 354-357

Hwang HS, Boluyt MO, Converso K, Russell MW, Bleske BE. Effects of hawthorn on the progression of heart failure in a rat model of aortic constriction. *Pharmacotherapy* (2009), 29(6): 639-648

Idris-Khodja N, Auger C, Koch E, Schini-Kerth VB. Crataegus special extract WS<sup>(®)</sup>1442 prevents aging-related endothelial dysfunction. *Phytomedicine* (2012), 19(8-9): 699-706

Irion H (Hrsg.). Drogisten-Lexikon. Ein Lehr- und Nachschlagebuch. Zweiter Band. Springer-Verlag Berlin/Göttingen/Heidelberg 1955, 1392-1393

Jayachandran KS, Khan M, Selvendiran K, Devaraj SN, Kuppusamy P. Crataegus oxycantha extract attenuates apoptotic incidence in myocardial ischemia-reperfusion injury by regulating Akt and HIF-1 signaling pathways. *Journal of Cardiovascular Pharmacology* (2010), 56(5): 526-531

Kaul R. Der Weißdorn. Botanik, Inhaltsstoffe, Qualitätskontrolle, Pharmakologie, Toxikologie und Klinik. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1998, 16-22

Koch E, Spörl-Aich G. Oral treatment with *Crataegus* special extract WS 1442 inhibits cardiac hypertrophy in rats with DOCA-salt or aortic banding induced hypertension. *Planta Medica* 2006, 72:1061

Koch E, Malek FA. Standardized Extracts from Hawthorn Leaves and Flowers in the Treatment of Cardiovascular Disorders – Preclinical and Clinical Studies. *Planta Medica* 2011, 77: 1123-1128

Kraft K. Phytotherapeutika – Welche sind am besten untersucht? *Internistische Praxis* (2006), 46(3): 657-664

Kraft K, Hobbs C. Pocket Guide to Herbal Medicine. Georg Thieme Verlag 2004, 132-133

Les Cahier de l'Agence N°3: Médicaments à base de plantes. Agence du Médicament, Paris 1998, 1-88

Leuchtgens H. Crategus-Spezialextrakt WS 1442 bei Herzinsuffizienz NYHA II. [The *Crataegus* special extract WS 1442 in patients with cardiac insufficiency NYHA II.] *Fortschritte der Medizin* 1993, 111(20/21):352-354

Liang M, Xu W, Zhang W, Zhang C, Liu R, Shen Y et al. Quantitative LC/MS/MS method and in vivo pharmacokinetic studies of vitexin rhamnoside, a bioactive constituent on cardiovascular system from hawthorn. *Biomedical chromatography: BMC* (2007), 21(4): 422-429

List PH, Hörhammer L. (editors) Hagers Handbuch der Pharmazeutischen Praxis. Vol. 4. Springer Verlag, Berlin - Heidelberg – New York, 1973, 324-331

Ma LY, Liu RH, Xu XD, Yu MQ, Zhang Q, Liu HL. The pharmacokinetics of C-glycosyl flavones of Hawthorn leaf flavonoids in rat after single dose oral administration. *Phytomedicine* (2010), 17(8-9): 640-645

Madaus G. Lehrbuch der biologischen Heilmittel. Vol. 2. Georg Olms Verlag. Hildesheim - New York 1976 (reprint from Madaus G 1938), 1113-1121

Momekov G, Benbassat N. Pharmacological properties of Hawthorn leaf and flower as a cardiovascular agent. *Pharmacria* 2013, 60(1): 24-36

O'Conolly M, Bernhöft G, Bartsch G. Behandlung älterer, multimorbider Patienten mit stenokardischen Beschwerden. *Therapiewoche* 1987, 37:3587-3600

O'Conolly M, Jansen W, Bernhöft G, Bartsch G. Behandlung der nachlassenden Herzleistung. [Treatment of decreasing cardiac performance (NYHA Stages I to II) in advanced age with standardized *Crataegus* extract.] *Fortschritte der Medizin* 1986, 104(42):805-808

Ripperger W. Grundlagen zur praktischen Pflanzenheilkund. Hippocrates-Verlag HmbHerlag Georg Thieme, Stuttgart-Leipzig 1937, 272-274

Rote Liste 1949. Verzeichnis pharmazeutischer Spezialextrakte. Arbeitsgemeinschaft Pharmazeutische Industrie – Frankfurt a.M. Editio Cantor K.G., Aulendorf i. Württ. 1949, 209

Schlegelmilch R, Heywood R. Toxicity of *Crataegus* (hawthorn) extract (WS 1442). *Journal of the American College of Toxicology* 1994, 13(2):103-111

Schmidt U, Kuhn U, Ploch M, Hübner WD. Wirksamkeit des Extraktes LI 132 (600 mg/Tag) bei achtwöchiger Therapie. [Efficacy of the hawthorn extract LI 132 (600 mg/d) during eight week's treatment.] *Münchener medizinische Wochenschrift* 1994, 136(Suppl. 1):13-19

Schmidt-Schweda S, Burstin JV, Möllmann H, Wollner S, Holubarsch C. Der positiv inotrope Effekt des *Crataegus* Spezialextrakts WS 1442 in isolierten Myozyten aus menschlichem Vorhof- und Ventrikelmyokard wird vorwiegend durch oligomere Procyanidine vermittelt. *Zeitschrift für Kardiologie* 2000; 98 (Suppl):164

Schulz H. Vorlesungen über Wirkung und Anwendung der deutschen Arzneipflanzen. Verlag Georg Thieme, Leipzig 1919, 254

Schwinger RHG, Pietsch M, Frank K, Brixius K. *Crataegus* special extract WS 1442 increases force of contraction in human myocardium cAMP-independently. *Journal of Cardiovascular Pharmacology* 2000, 35(5):700-707

Sendker J, Petereit F, Lautenschläger M, Hellenbrand N, Hensel A. Phenylpropanoid-substituted procyanoindins and tentatively identified procyanoindin glycosides from hawthorn (*Crataegus* spp.). *Planta Medica* 2013, 79: 45-51

Shatoor AS, Soliman H, Al-Hashem F, El-Gamal B, Othman A, El-Menshawy N. Effect of Hawthorn (*Crataegus aronia* syn. *Azarolus* (L)) on platelet function in albino wistar rats. *Thrombosis Research* 2012, 130:75-80

Tankanow R, Tamer HR, Streetman DS, Smith SG, Annesley T, Aaronson KD, Bleske BE. Interaction study between digoxin and a preparation of hawthorn (*Crataegus oxyacantha*). *Journal of Clinical Pharmacology* 2003, 43:637-642

Tassell MC, Kingston R, Gilroy D, Lehane M, Furey A. Hawthorn (*Crataegus* spp.) in the treatment of cardiovascular disease. *Pharmacognosy Reviews* 2010, 4(7):32-41

Tauchert M. Efficacy and safety of *Crataegus* extract WS 1442 in comparison with placebo in patients with chronic stable New York Heart Association class-III heart failure. *American Heart Journal* 2002, 143(5):910-915

Tauchert M, Gildor A, Lipinski J. Einsatz des hochdosierten Crataegusextraktes WS 1442 in der Therapie der Herzinsuffizienz Stadium NYHA II. [High-dose *Crataegus* (hawthorn) extract WS 1442 for the treatment of NYHA class II heart failure patients.] *Herz* 1999, 24(6):465-474

Tauchert M, Ploch M, Hübner WD. Wirksamkeit des Weißdorn-Extraktes LI 132 im Vergleich mit Captopril. [Effectiveness of the hawthorn extract LI 132 compared with the ACE inhibitor captopril.] *Münchener medizinische Wochenschrift* 1994, 136(Suppl. 1):27-33

Veveris M, Koch E, Chatterjee SS. Crataegus special extract WS 1442 improves cardiac function and reduces infarct size in a rat model of prolonged coronary ischemia and reperfusion. *Life Sciences* (2004), 74(15): 1945-1955

Vogel JHK, Bolling SF, Costello RB, Guarneri EM, Krucoff MW, Longhurst JC et al. Integrating complementary medicine into cardiovascular medicine. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (Writing Committee to Develop an Expert Consensus Document on Complementary and Integrative Medicine). *Journal of the American College of Cardiology* 2005; 46(1):184-221

Weikl A, Assmus KD, Neukum-Schmidt A, Schmitz J, Zapfe G, Noh HS, Sigrist J. *Crataegus-Spezialextrakt WS 1442*. [Objective confirmation of the efficacy of *Crataegus-Spezialextrakt* (a special *Crataegus* extract) WS 1442 in patients with cardiac insufficiency (NYHA II)] *Fortschritte der Medizin* 1996; 114(24):291-296

Weikl A, Noh HS. Der Einfluss von Crataegus bei globaler Herzinsuffizienz. *Herz + Gefäß* 1992; 11:516-524

WHO. *Folium cum Flore Crataegi*. WHO Monographs on Selected Medicinal Plants. Geneva: World Health Organization 2002:66-82

Wichtl M. *Teedrogen*. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1984, 358-360

Williamson E, Driver S, Baxter K. (editors) Stockley's herbal medicines interactions. A guide to the interactions of herbal medicines. 2<sup>nd</sup> ed. Pharmaceutical Press, London 2013, 283-284

Yao M, Ritchie HE, Brown-Woodman PD. A reproductive screening test of hawthorn. *Journal of Ethnopharmacology* 2008; 118:127-132

Zapfe jun. G. Clinical efficacy of *Crataegus* extract WS 1442 in congestive heart failure NYHA class II. *Phytomedicine* 2001; 8(4):262-266

Zhang DL, Zhang YT, Yin JJ, Zhao BL. Oral administration of *Crataegus* flavonoids protects against ischemia/reperfusion brain damage in gerbils. *Journal of Neurochemistry* (2004); 90(1): 211-219

Zick SM, Vautaw BM, Gillespie B, Aaronson KD. Hawthorn extract randomized blinded chronic heart failure (HERB CHF) trial. *European Journal of Heart Failure* 2009; 11:990-999