



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

5 April 2016  
EMA/HMPC/378548/2014  
Committee on Herbal Medicinal Products (HMPC)

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

Final

**The European Medicines 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, *et al.* Phytochemical analysis, antioxidant activity and hypotensive effect of algerian azarole (*Crataegus azarolus* L.) leaves extracts. *Res J Pharm, Biol Chem Sci* 2014, 5(2):286-305

Ammon HPT, Händel M. *Crataegus*, Toxikologie und Pharmakologie. Teil III: Pharmakodynamik und Pharmakokinetik. [Crataegus, Toxicology and Pharmacology. Part III: Pharmacodynamics and Pharmacokinetics.] *Planta Med* 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 Complement Altern Med* 2012, 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 Verlag, Berlin Heidelberg

Blaschek W, Hilgenfeldt U, Holzgrabe U, Reichling J, Ruth P, Schulz V, editors. HagerROM 2013. Crataegi folium cum flore (Weißdornblätter mit Blüten). Hagers Enzyklopädie der Arzneistoffe und Drogen. Springer Verlag, Berlin Heidelberg

Bleske BE, 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. *Med Sci Monit* 2007, 13(12):255-258

Bödighheimer 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.] *Münch Med Wochenschr* 1994, 136(Suppl. 1):7-11

Bradley P, editor. British Herbal Compendium – A handbook of scientific information on widely used plant drugs. Vol 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, *et al.* Crataegus special extract WS 1442 induces an endothelium-dependent, NO-mediated vasorelaxation via eNOS-phosphorylation at serine 1177. *Cardiovasc Drugs Ther* 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<sup>®</sup> 1442 targets the cAMP/Rap1 pathway. *J Mol Cell Cardiol* 2012, 52(1):196-205
- Chang Q, Zuo Z, Harrison F, Chow MS. Hawthorn. *Journal of Clinical Pharmacology* 2002, 42(6):605-612
- Chang Q, Zuo Z, Ho WK, Chow MS. Comparison of the pharmacokinetics of hawthorn phenolics in extract versus individual pure compound. *J Clin Pharmacol* 2005a, 45(1):106-112
- Chang WT, Dao J, Shao ZH. Hawthorn: Potential roles in cardiovascular disease. *Am J Chin Med* 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
- CPMP/EWP/235/95 Rev. 1. Committee for proprietary medicinal products (CPMP) Note for guidance on clinical investigation of medicinal products for the treatment of cardiac failure. Available at: [www.ema.europa.eu/ema/pages/includes/document/open\\_document.jsp?webContentId=WC500003364](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003364) Accessed 01/2016
- Dalli E, Colomer E, Tormos MC, Cosin-Sales J, Milara J, Esteban E, *et al.* *Crataegus laevigata* decreases neutrophil elastase and has hypolipidemic effect: a randomized, double-blind, placebo-controlled trial. *Phytomedicine* 2011a, 18(8-9):769-775
- Dalli E, Vallés J, Cosin-Sales J, Santos MT, Moscardó A, Milara J, *et al.* Effects of hawthorn (*Crataegus laevigata*) on platelet aggregation in healthy volunteers. *Thromb Res* 2011b, 128(4):398-400
- Daniele C, Mazzanti G, Pittler MH, Ernst E. Adverse event profile of *Crataegus spp.*: A systematic review. *Drug Saf* 2006, 29(6):523-535
- Dasgupta A, Kidd L, Poindexter BJ, Bick RJ. Interference of hawthorn on serum digoxin measurements by immunoassays and pharmacodynamic interaction with digoxin. *Arch Pathol Lab Med* 2010, 134:1188-1192
- Dood KP, Frey AD, Geisbuhler TP. The effect of Hawthorn extract on the coronary flow. *J Evid Based Complementary Altern Med* 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> ed. Church Street Books, Nassau NY 2000b, 109-111
- ESC. Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2012, 33:1787-1847
- European Pharmacopoeia 8<sup>th</sup> ed. 2014 (2014a) (8.1). Council of Europe. 01/2010:1432
- European Pharmacopoeia 8<sup>th</sup> ed. 2014 (2014b) (8.1). Council of Europe. 01/2008:1864
- European Pharmacopoeia 8<sup>th</sup> ed. 2014 (2014c) (8.1). Council of Europe. 01/2010:1865
- Fischer K, Jung F, Koscielny J, Kiesewetter H. Crataegus-Extrakt vs. Methyldigoxin. Einfluss auf Rheology und Mikrozirkulation bei 12 gesunden Probanden. [Crataegus Extract vs. medigoxin. Effects on rheology and microcirculation in 12 healthy volunteers.] *Münch Med Wochenschr* 1994, 136(Suppl. 1):35-38
- Förster A, Förster K, Bühring M, Wolfstädter HD. Crataegus bei mäßig reduzierter linksventrikulärer Auswurfraction. [Crataegus for moderately reduced left ventricular ejection fraction.] *Münch Med Wochenschr* 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, Mamtani R. Alternative and complementary medical approaches in the prevention and treatment of cardiovascular disease. *Curr Probl Cardiol* 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. *J Atheroscler Res* 2010, 211(2):409-417
- Gehes Codex. Codex der pharmazeutischen Spezialpräparate mit Angaben über Zusammensetzung, Indikationen, Zuberieutngsformen 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, editors. PDR for herbal medicines. 4<sup>th</sup> ed. Thomson Healthcare Inc., Montvale 2007, 279-284
- Härtel S, Kutzner C, Westphal E, Limberger M, Burkart M, Ebner-Priemer U, *et al.* Effects of Endurance Exercise Training and Crataegus Extract WS<sup>®</sup>1442 in Patients with Heart Failure with Preserved Ejection Fraction – A Randomized Controlled Trial. *Sports* 2014, 2:59-75
- 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 Universität 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. *Eur J Heart Fail* 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, editor. 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 oxyacantha* extract attenuates apoptotic incidence in myocardial ischemia-reperfusion injury by regulating Akt and HIF-1 signaling pathways. *J Cardiovasc Pharmacol* 2010, 56(5):526-531
- Kanyonga MP, Faouzi MYA, Zellou A, Essassi M, Cherrah Y. Effects of methanolic extract of *Crataegus oxyacantha* on blood homeostasis in rat. *J Chem Pharm Res* 2011, 3(3):713-717
- 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 Med* 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 Med* 2011, 77:1123-1128
- Koller M, Lorenz W, Aubke W, Jensen A, Gerlach FM, Kuhl J, *et al.* Weißdorn-Spezialextrakt in der Therapie früher Stadien der KHK-assoziierten Herzinsuffizienz. *MMW Fortschr Med* 2005, 147(4):159-164
- 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.] *Fortschr Med* 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. *Biomed Chromatogr* 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. *Pharmacia* 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.] *Fortschr Med* 1986, 104(42):805-808

Pittler MH, Guo R, Ernst E. Hawthorn extract for treating chronic heart failure (review). *Cochrane Database Syst Rev* 2008, Issue 1. Art. No. CD005312

Ripperger W. Grundlagen zur praktischen Pflanzenheilkund. Hippokrates-Verlag GmbH Verlag 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). *J Am Coll Toxicol* 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.] *Münch Med Wochenschr* 1994, 136(Suppl. 1):13-19

Schmidt-Schweda S, Burstin JV, Möllmann H, Wollner S, Holubarsch C. Der positiv inotrope Effekt des Cratagus Spezialextrakts WS 1442 in isolierten Myozyten aus menschlichem Vorhof- und Ventrikelmyokard wird vorwiegend durch oligomere Procyanidine vermittelt. *Z Kardiol* 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. *J Cardiovascular Pharmacol* 2000, 35(5):700-707

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

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

Tankanow R, Tamer HR, Streetman DS, Smith SG, Annesley T, Aaronson KD, *et al.* Interaction study between digoxin and a preparation of hawthorn (*Crataegus oxyacantha*). *J Clin Pharmacol* 2003, 43:637-642

Tassell MC, Kingston R, Gilroy D, Lehane M, Furey A. Hawthorn (*Crataegus* spp.) in the treatment of cardiovascular disease. *Pharmacogn Rev* 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. *Am Heart J* 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.] *Münch Med Wochenschr* 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 Sci* 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). *J Am Coll Cardiol* 2005 46(1):184-221
- Weigl A, Assmus KD, Neukum-Schmidt A, Schmitz J, Zapfe G, Noh HS, *et al.* 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).] *Fortschr Med* 1996, 114(24):291-296
- Weigl A, Noh HS. Der Einfluss von Crataegus bei globaler Herzinsuffizienz. *Herz + Gefäß* 1992, 11:516-524
- WHO. WHO Monographs on Selected Medicinal Plants. Folium cum Flore Crataegi. World Health Organization. Geneva 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. *J Ethnopharmacol* 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
- Zick SM, Vautaw BM, Gillespie B, Aaronson KD. Hawthorn extract randomized blinded chronic heart failure (HERB CHF) trial. *Eur J Heart Fail* 2009, 11:990-999