20 September 2016
EMA/HMPC/278220/2015
Committee on Herbal Medicinal Products (HMPC)

List of references supporting the assessment of *Silybum marianum* (L.) Gaertn., fructus

Draft

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.

Abenavoli L, Capasso R, Milic N, Capasso F. Milk thistle in liver diseases: past, present and future. *Phytother Res* 2010, 24:1423-1432

Ahmad N, Gali H, Javed S, Agarwal R. Skin cancer chemopreventive effects of a flavonoid antioxidant silymarin are mediated via impairment of receptor tyrosine kinase signaling and perturbation in cell cycle progression. *Biochem Biophys Res Comm* 1998, 247:294-301

Ahmed-Belkacem A, Ahnou N, Barbotte L, Wychowski C, Pallier C, Brillet R, *et al*. Silibinin and related compounds are direct inhibitors of hepatitis C virus RNA-dependent RNA polymerase. *Gastroenterol* 2010, 138:1112–1122

Allain H, Schück S, Lebreton S, Strenge-Hesse A, Braun W, Gandon JM, *et al*. Aminotransferase levels and silymarin in de novo tacrine-treated patients with Alzheimer´s disease. *Dement Geriatr Cogn Disord* 1999, 10:181-185

Anderson D, Dobrzynska MM, Yu TW. Modulating effects of silymarin and myricetin on food mutagens and doxorubicin in assays with different genetic endpoints. *J Environm Pathol Toxicol Oncol* 1997a, 16:313-327

Anderson D, Basaran N, Dobrzynska MM, Basaran AA, Yu TW. Modulating effects of flavonoids on food mutagens in human blood and sperm samples in the comet assay. *Teratogenesis Carcinog Mutagen* 1997b, 17:45-58

Angulo P, Jorgensen RA. Silymarin in the treatment of patients with primary sclerosing cholangitis: an open-label pilot study. *Dig Dis Sci* 2008, 53:1716-1720

Bannwart CF, Peracollo JC, Nakaira-Takahagi E, Peracoli MTS. Inhibitory effect of silibinin on tumour necrosis factor alpha and hydrogen peroxide production by human monocytes. *Nat Prod Res* 2010, 24:1747-1757

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Barnes J, Anderson LA, Phillipson JD. Herbal Medicines. 3rd ed. (First ed. 1996) Milk Thistle, Pharmaceutical Press, London 2007, 429-435

Bares JM, Berger J, Nelson JE, Messner DJ, Schitdt S, Standish LJ, *et al*. Silybinin treatment is associated with reduction in serum ferritin in patients with chronic hepatitis C. *J Clin Gastroenterol* 2008, 42:937-944

Benda L, Dittrich H, Ferenzi P, Frank H, Wewalka F.The influence of therapy with silymarin on the survival rate of patients with liver cirrhosis. *Wien Klin Wochenschr* 1980, 92(19):678-683

Blumenthal M, Busse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW, *et al*, editors. Klein S, Rister RS (trans.). In: *The Complete German Commission E Monographs—Therapeutic Guide to Herbal Medicines*. Austin, TX: American Botanical Council; Boston: Integrative Medicine Communication; 1998, 11:169–170

Blumenthal M, Goldberg A, Brinckmann J, editors. Milk Thistle Fruit. In: *Herbal Medicine: Expanded Commission E Monographs*. Newton, MA: Integrative Medicine Communications 2000, 257–63

Boari C, Montanari FM, Galletti GP, Rizzoli D, Baldi E, Caudarella R, *et al*. Toxic occupational liver diseases. Therapeutic effects of silymarin. *Minerva Med* 1981, 72(40):2679-2688

Boigk G, Stroedter L, Herbst H, Waldschmidt J, Riecken EO, Schuppan D. Silymarin retards collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct obliteration in rats. *Hepatology* 1997, 26(3):643-649

Boisio E, Benelli C, Pirola O. Effect of the flavonolignans of *Silybum marianum* L. on lipid peroxidation in rat liver microsomes and freshly isolated hepatocytes. *Pharmacology Research* 1992, 25:147-154

Bradley P. The British Herbal Compendium. Vol 2. British Herbal Medicine Association, 2006

Bruneton J. Pharmacognosy, Phytochemistry Medicinal Plants. 2nd ed. Lavoisier Publishing, 1999

Bunout D, Hirsch S, Petermann M, de la Maza MP, Silva G, Kelly M *et al*. [Controlled study on the effect of silimarin in alcoholic liver disease.] [Spanish]. *Rev Med Chile* 1992, 120:1370–1375

Butorova VL, Tsibizova, Kalinin AI. Possibilities of legalon application in nonalcoholic fatty liver disease. *Expe Clin Gastroenterol* 2010, 3:85-91

Campos R, Garrido A, Guerra A. Silybin dihemisuccinate protects against hepatic lipid peroxidation induced by acetaminophen on rat liver. *Planta Med* 1989, 55:417-419

Cardo mariano, extracto seco refinado y normalizado de - Silybi mariani extractum siccum raffinatum et normatum (Spanish Pharmacopoeia, 5th Edition 2015; Ref 01/2008, 2071)

Cardo mariano, fruto de (Spanish Pharmacopoeia, 5th Edition 2015; Ref 01/2008, 1860)

Cardui mariae (o mariani) fructus (BP 1996): Dried ripe fruits of Silybum marianum (L.) Gaertn.

Chlopcíková S, Psotová J, Miketová P, Simánek V. Chemoprotective effect of plant phenolics against anthracycline-induced toxicity on rat cardiomyocytes. Part I. Silymarin and its flavonolignans. *Phytother Res* 2004, 18(2):107-110

Comelli MC, Mengs U, Schneider C, Prosdocimi M. Toward the definition of the mechanism of action of silymarin: activities related to cellular protection from toxic damage induced by chemotherapy. *Integr Cancer Ther* 2007, 6:120-129

Crocenzi FA, Pellegrino JM, Sánchez Pozzi EJ, Mottino AD, Rodríguez Garay EA, Roma MG. Effect of Silymarin on Biliary Bile Salt Secretion in the Rat. *Biochemical Pharmacology* 2000, 59:1015–1022

Crocenzi FA, Sánchez Pozzi EJ, Pellegrino JM, Rodríguez Garay EA, Mottino AD, Roma MG. Preventive effect of silymarin against taurolithocholate-induced cholestasis in the rat. *Biochem Pharmacol* 2003, 66:355-364

Crocenzi FA, Basiglio CL, Perez LM, Portesio MS, Pozzi EJ, Roma MG. Silibinin prevents cholestasis-associated retrieval of the bile salt export pump, Bsep, in isolated rat hepatocyte couplets: Possible involvement of cAMP. *Biochem Pharmacol* 2005, 69:1113-1120

Davila JC, Lenherr A, Acosta D. Protective effect of flavonoids on drug-induced hepatotoxicity in vitro. *Toxicol* 1989, 57(3):267-286

Deak G, Muzes G, Lang I, Niederland V, Nekam K, Gonzalez-Cabello R, et al. Immunomodulator effect of silymarin therapy in chronic alcoholic liver diseases. *Orvosi hetilap* 1990, 131(24):1291-1292, 1295-1296

Dehmlow C, Erhard J, de Groot H. Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin. *Hepatology* 1996, 23(4):749–754

Dermarderosian AA. The Review of Natural Products. 1st ed. Facts and Comparisons: St. Louis, Missouri 2001

Di Pierro F, Callegari A, Carotenuto D, Tapia MM. Clinical efficacy, safety and tolerability of BIO-C (micronized Silymarin) as a galactogogue. *Acta Biomed* 2008, 205-210

DiMario F, Farini R, Okolicsanyi L, Naccarato R. The Effects of Silymarin on the Liver Function Parameters of Patients with Alcohol-Induced Liver Disease: A Double Blind Study. In: de Ritis F, Csomos G, Braatz R, editors. *Der Toxischmetabolische Leberschaden*. Lübeck, Germany: Hans. Verl.-Kontor 1981, 54–58

Dunnick JK, Nyska A. The Toxicity and Pathology of Selected Dietary Herbal Medicines. *Toxicol Pathol* 2013, 41:374-386

Dunnick JK, Singh B, Nyska A, Peckham J, Kissling GE, Sanders JM. Investigating the Potential for Toxicity from Long-Term Use of the Herbal Products, Goldenseal and Milk Thistle. *Toxicol Pathol* 2011a, 39:398-409

Dunnick JK, Nyska A, Bishop JB, Bucher JR, Chhabra RS, Foster PM *et al*., Toxicology and carcinogenesis studies of milk thistle extract (CAS No. 84604-20-6) in F344/N rats and B6C3F1 mice (Feed Studies). *National Toxicology Program Technical Report* 2011b, 565:1-177

Duthie SJ, Collins AR, Duthie GG, Dobson VL. Quercetin and myricetin protect against hydrogen peroxide-induced DNA damage (strand breaks and oxidised pyrimidines) in human lymphocytes. *Mutat Res* 1997, 393(3):223-231

Dvorak Z, Kosina P, Walterova D, Simanek V, Bachleda P, Ulrichova J. Primary cultures of human hepatocytes as a tool in cytotoxicity studies: cell protection against model toxins by flavonolignans obtained from *Silybum marianum*. *Toxicol Letters* 2003, 137:201-212

El-Kamary SS, Shardell MD, Adel-Hamid M, Ismail S, El-Ateek M, Metwally M, *et al*. A randomized controlled trial to assess the safety and efficacy of silymarin on symptoms, signs and biomarkers of acute hepatitis. *Phytomedicine* 2009, 16:391-400

El-Shitany MA, Hegazi S, El-Desoku K. Evidences for antiosteoporotic and selective estrogen receptor modulator activity of silymarin compared with ethinylestradiol in ovariectomized rats. *Phytomedicine* 2010, 17:116-125

ESCOP Monographs 2nd ed. Milk thistle. European Scientific Cooperative on Phytotherapy, editor. Thieme, Stuttgart 2009, 229-248

European Pharmacopoeia 7th ed. Milk Thistle. Council of Europe. 1860

European Pharmacopoeia 7th ed. Milk Thistle extract. Council of Europe. 2071

Favari L, Pérez-Alvarez V. Comparative effects of colchicine and silymarin on CCl4-chronic liver damage in rats. *Arch Med Res* 1997, 28(1):11-17

Fehér J, Deák G, Müzes G, Láng I, Niederland V, Nékám K, *et al*. Liver protection of silymarin therapy in chronic alcoholic liver diseases. *Orv Hetil* 1989, 130:2723-2727

Ferenci P, Dragosics B, Dittrich H, Frank H, Benda L, Lochs H, *et al*. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatology* 1989, 9:105-113

Filipe PM, Fernandes AC, Silva JN, Freitas JP, Manso CF. Effect of silibinin on oxidative damage of blood constituents. *C R Seances Soc Biol Fil* 1997, 191(5-6):821-835

Fintelmann V, Albert A. The therapeutic activity of Legalon® in toxic hepatic disorders demonstrated in a double-blind trial. [Nachweis der therapeutischen Wirksamkeit von Legalon bei toxischen Lebererkrankungen im Doppelblindversuch]. *Therapiewoche* 1980, 30:5589-5594

Fintelmann V. Serumcholinesterase and other liver enzymes in postsurgical conditions [Postoperatives Verhalten der Serumcholinesterase und anderer Leberenzyme]. *Med Klinik* 1973, 68:809-815

Freedman ND, Curto TM, Morishima C, Seeff LB, Goodman ZD, Wright EC, *et al*. HALT-C Trial Group. Silymarin use and liver disease progression in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis trial. *Aliment Pharmacol Ther* 2011, 33(1):127–137

French Pharmacopoeia for homeopathic preparations. 1989

Fried MW, Navarro VJ, Afdhal N, Belle SH, Wahed AS, Hawke RL, *et al*. Effect of Silymarin (Milk Thistle) on Liver Disease in Patients With Chronic Hepatitis C Unsuccessfully Treated With Interferon Therapy: A Randomized Controlled Trial. *JAMA* 2012, 308(3):274–282

Fuchs EC, Gressner AM, Weyhenmeyer R, Weiner OH. Effects of Silibinin and Silibininderivates on Hepatic Stellate Cells and Myofibroblasts. *Hepatology* 1995, 22:866A

Fuchs EC, Weyhenmeyer R, Weiner OH. Effects of silibinin and of a synthetic analogue on isolated rat hepatic stellate cells and myofibroblasts. *Arzneimforsch Drug Res* 1997, 47:1383-1387

Galhardi F, Mesquita K, Monserrat JM, Barros DM. Effect of silymarin on biochemical parameters of oxidative stress in aged and young rat brain. *Food Chem Toxicol* 2009, 47:2655–2660

Garrido A, Fairlie J, Guerra R, Campos R, Valenzuela A. The flavonoid silybin ameliorates the protective effect of ethanol on acetaminophen hepatotoxicity. *Res Commun Substances Abuse* 1989, 10:193-196

Gažák R, Sedmera P, Vrbacký M, Vostálová J, Drahota Z, Marhol P, *et al*. Molecular mechanisms of silybin and 2,3-dehydrosilybin antiradical activity—role of individual hydroxyl groups. *Free Rad Biol & Med* 2009, 46:745–758

Gažák R, Svobodova A, Psotova J, Sedmera P, Prikrylova V, Walterova V, *et al*. Oxidised derivatives of silybin and their antiradical and antioxidant activity. *Bioorg Med Chem* 2004, 12(21):5677–5687

Gebhardt R. Oxidative stress, plant-derived antioxidants and liver fibrosis. *Planta Med* 2002, 68(4): 289-296

Gharagozloo M, Velardi E, Bruscoli S, Agostini M, Di Sante M , Donato V, *et al*. Silymarin suppress CD4+ T cell activation and proliferation: Effects on NF-kappaB activity and IL-2 production. *Pharmacol Res* 2010, 61:405–409

Gharagozloo M, Moayedi B, Zakerinia M, Hamidi M, Karimi M, Maracy M, *et al*. Combined therapy of silymarin and desferrioxamine in patients with β-thalassemia major: a randomized double-blind clinical trial. *Fundamental and Clinical Pharmacology* 2009, 23:359-365

Gharagozloo M, Karimi M, Amirghofran Z. Immunomodulatory effects of silymarin in patients with β-thalassemia major. *International Immunopharmacology* 2013a, 16:243–247

Gharagozloo M, Javid EN, Rezaei A, Mousavizadeh K. Silymarin Inhibits Cell Cycle Progression and mTOR Activity in Activated Human T Cells: Therapeutic Implications for Autoimmune Diseases. *Basic & Clinical Pharmacology & Toxicology* 2013b, 112:251–256

Gharagozloo M, Jafari S, Esmaeil N, Javid EN, Bagherpour B, Rezaei A. Immunosuppressive Effect of Silymarin on Mitogen-Activated Protein Kinase Signalling Pathway: the Impact on T Cell Proliferation and Cytokine Production. *Basic & Clinical Pharmacology & Toxicology* 2013c, 113:209–214

Gordon A, Hobbs DA, Bowden DS, Bailey MJ, Mitchell J, Francis AJP, *et al*. Effects of Silybum marianum on serum hepatitis C virus RNA, alanine aminotransferase levels and well-being in patients with chronic hepatitis C. *J Gastroenterol Hepatol* 2006, 21(1):275-280

Grattagliano I, Ubaldi E, Bonfrate L, Portincasa P. Management of liver cirrhosis between primary care and specialists. *World J Gastroenterol* 2011, 17(18):2273-2282

Hahn G, Lehmann H, Kürten M, Uebel H, Vogel G. Zur Pharmakologie und Toxikologie von Silymarin, des antihepatotoxischen Wirkprinzipes aus Silybum marianum (L.) Gaertn. *Arzneim Forsch Drug Res 1968*, 18:698-704

Hajiaghamohammadi AA, Ziaee A, Oveisi S, Masroor H. Effects of Metformin, Pioglitazone, and Silymarin Treatment on Non- Alcoholic Fatty Liver Disease: A Randomized Controlled Pilot Study. *Hepatitis Monthly* 2012, 12(8):e6099

Haková H, Misúrová E. Therapeutical effect of silymarin on nucleic acids in the various organs of rats after radiation injury. *Radiats Biol Radioecol* 1996, 36(3):365-370

Hammeri H, Pichler O, Studlar M. Über die Objektivierung der Silymarinwirkung bei Lebererkrankungen. *Med Klinik* 1971, 66(36):1204-1208

Hashemi SJ, Hajiani E, Sardabi EH. A Placebo-Controlled Trial of Silymarin in Patients with Nonalcoholic Fatty Liver Disease. *Hepatitis Monthly* 2009, 9(4):265-270

Homeopathic Pharmacopoeia of India (Vol. I, pp. 94, 1971) (Varma *et al*., 1980)

Hruby C. Silibinin in the treatment of death cap fungus poisoning. *Forum* 1984, 6:23–26

Hruby K, Csomos G, Fuhrmann M, Thaler H. Chemotherapy of *Amanita phalloides* poisoning with intravenous silibinin. *Hum Toxicol* 1983, 2:183-195

Huseini HF, Larijani B, Heshmat R, Fakhrzadeh H, Radjabipour B, Toliat T, *et al*. The efficacy of *Silybum marianum* (L.) Gaertn. (Silymarin) in the treatment of type II diabetes: A randomized, double-blind, placebo-controlled, clinical trial. *Phytother Res* 2006, 20(12):1036-1039

Hussain SA. Silymarin as an adjunct to glibenclamide therapy improves long-term and postprandial glycemic control and body mass index in type 2 diabetes. *J Med Food* 2007, 10(3):543-547

Hutchinson C, Bomford A, Geissler CA. The iron-chelating potential of silybin in patients with hereditary haemochromatosis. *Eur J Clin Nutr* 2010, 64(10):1239-1241

Jeong DH, Lee GP, Jeong WI, Do SH, Yang HJ, Yuan DW, *et al*. Alterations of mast cells and TGF-beta1 on the silymarin treatment for CCl(4)-induced hepatic fibrosis. *World J Gastroenterol* 2005, 11(8):1141-1148

Jia JD, Bauer M, Cho JJ, Ruehl M, Milani S, Boigk G, *et al*. Antifibrotic effect of silymarin in rat secondary biliary fibrosis is mediated by downregulation of procollagen a1(I) and TIMP-1. *Journal of Hepatology* 2001, 35:392–398

Kalantari H, Shahshahan Z, Hejazi M, Ghafghazi T, Sebghatolahi V. Effects of *Silybum marianum* on patients with chronic hepatitis C. *J of research in Medical Sciences* 2011, 6(3):287-290

Kang JS, Park S, Yang K, Kima HM. Silymarin inhibits TNF-K-induced expression of adhesion molecules in human umbilical vein endothelial cells. *FEBS Letters* 2003, 550:89-93

Katiyar SK, Mantena SK, Meeran SM. Silymarin protects epidermal keratinocytes from ultraviolet radiation-induced apoptosis and DNA damage by nucleotide excision repair mechanism. *PLOS* 2011, 6:e21410

Kim YC, Kim EJ, Lee ED, Kim JH, Jang SW, Kim YG. Comparative bioavailability of silibinin in healthy male volunteers. *Int J Clin Pharmacol Ther* 2003, 41:593-596

Kim S, Choi JH, Lim HI, Lee SK, Kim WW, Kim JS, *et al*. Silibinin prevents TPA-induced MMP-9 expression and VEGF secretion by inactivation of the Raf/MEK/ERK pathway in MCF-7 human breast cancer cells. *Phytomedicine* 2009, 16(6-7):573-580

Köksal E, Gülcin I, Beyza S, Sarikaya O, Bursal E. In vitro antioxidant activity of silymarin. *J Enzyme Inhib Med Chem* 2009, 24:395-405

Kröncke KD, Fricert G, Meier PJ, Gerok W, Wieland T, Kurz G. Alphaamanitin into hepatocytes. *J Biol Chem* 1986, 261:12562-12567

Kurz-Dimitrowa D. Preservation of liver function in psychiatric patients receiving long-term treatment with psychopharmaceuticals. [Leberschutzbehandlung psychiatrisch-neurologischer Patienten bei Langzeittherapie mit Psychopharmaka]. *Z Präklin Geriatr* 1971, 9:275-277

Ladas EJ, Kroll DJ, Oberlies NH, Cheng B, Ndao DH, Rheingold SR, *et al*. A randomized, controlled, double-blind, pilot-study of milk thistle for the treatment of hepatotoxicity in childhood acute lymphoblastic leukemia (ALL). *Cancer* 2010, 116(2):506-513

Láng I, Nékám K, Deák G, Müzes G, Gonzales-Cabello R, Gergely P, *et al*. Immunomodulatory and hepatoprotective effects of in vivo treatment with free radical scavengers. *Ital J Gastroenterol* 1990, 22(5):283-287

Lee D, Liu Y. Molecular structure and stereochemistry of Silybin A, silybin B, isosilybin A, and isosilybin B, isolated from *Silybum marianum* (Milk Thistle). *J Nat Prod* 2003, 66:1171-1174

Lettéron P, Labbe G, Degott C, Berson A, Fromenty B, Delaforge M, *et al*. Mechanism for the protective effects of silymarin against carbon tetrachloride-induced lipid peroxidation and hepatotoxicity in mice. *Biochem Pharmacol* 1990, 39:2027-2034

Lieber CS, Leo MA, Cao Q, Ren C, DeCarli LM. Silymarin retards the progression of alcohol-induced hepatic fibrosis in baboons. *Journal of Clinical Gastroenterology* 2003, 37(4):336-339

Lirussi F, Beccarello A, Zanette G, De Monte A, Donadon V, Velussi M, *et al*. Silybin-ß-cyclodextrin in the treatment of patients with diabetes mellitus and alcoholic liver disease. Efficacy study of a new preparation of an antioxidant agent. *Diab Nutr Metab* 2002, 15:222-231

Locher R Suter PM, Weyhenmeyer R, Vetter W. Inhibitory action of silibinin on low density lipoprotein oxidation. *Arzneimittelforschung* 1998, 48(3):236-239

Loguercio C, Festi D. Silybin and the liver: from basic research to clinical practice. *World J Gastroenterol* 2011, 17:2288–2301

Lucena MI, Andrade RJ, de la Cruz JP, Rodríguez-Mendizábal M, Blanco E, Sánchez de la Cuesta F. Effects of silymarin MZ-80 on oxidative stress in patients with alcoholic cirrhosis. Results of a randomized, double-blind, placebo-controlled clinical study. *Int J Clin Pharmacol Ther* 2002, 40(1):2-8

Magliulo E, Carosi PG, Minoli L, Gorini S. Studies on the regenerative capacity of the liver in rats subjected to partial hepatectomy and treated with silymarin. *Arzneimittelforschung* 1973, 23:161-167

Malekinejad H, Taheri-Broujerdi M, Moradi M, Tabatabaie SH. Silymarin potentiates the antinociceptive effect of morphine in mice. *Phytotherapy Research* 2011, 25(2):250–255

Malewicz B, Wang Z, Jiang C, Guo J, Cleary MP, Grande JP, *et al*. Enhancement of mammary carcinogenesis in two rodent models by silymarin dietary supplements. *Carcinogenesis* 2006, 27(9):1739-1747

Marena C, Lampertico M. Preliminary clinical development of silipide: A new complex of silybin in toxic liver disorders. *Planta medica* 1991, 57:124-125

Mariendistelfrüchtetrockenextrakt – Cardui mariae fructus extractum siccum (DAB 2003)

Martindale: The Extra Pharmacopoeia (29th ed). The Pharmaceutical Press, London, 2009

Materia Medica Vegetabilis (Steinmetz, 1997) for Herba Cardui Mariae (number 295)

Mehta RG, Moon RC. Characterization of effective chemopreventive agents in mammary gland *in vitro* using an initiation-promotion protocol. *Anticancer Res* 1991, 11(2):593-596

Mereish KA, Solow R. Effect of antihepatotoxic agents against microcystin-LR toxicity in cultured rat hepatocytes. *Pharm Res* 1990, 7(3):256-259

Mereish KA, Bunner DL, Ragland DR, Creasia DA. Protection against microcystin-LR-induced hepatotoxicity by silymarin: biochemistry, histopathology, and lethality. *Pharm Res* 1991, 8(2):273-277

Meroni PL, Barcellini W, Borghi MO, Vismara A, Ferraro G, Ciani D, *et al*. Silybin inhibition of human T-lymphocyte activation. *Int J Tissue React* 1988, 10(3):177-181

Miadonna A, Tedeschi A, Leggieri E, Lorini M, Froldi M, Zanussi C. Effects of silybin on histamine release from human basophil leucocytes. *Br J Clin Pharmac* 1987, 24:747-752

British Herbal Compendium 2006. Milk thistle fruit, 282-289

Miller CH, Hamilton SM; Teel RW. Effects of compounds of plant origin on the mutagenicity and metabolism of the tobacco-sepecific nitrosamine NNK. *Phytotherapy res* 1994, 8:342-347

Mills S, Bone K, editors. St Mary's thistle. In: Principles and Practice of Phtytotherapy, Modern Herbal Medicine. Churchill Livingstone, London, 2000, 553-562

Mills E, Wilson K, Clarke M, Foster B, Walker S, Rachlis B, *et al*. Milk thistle and indinavir: a randomized controlled pharmacokinetics study and meta-analysis. *Eur J Clin Pharmacol* 2005, 61:1-7

Moayedi B, Gharagozloo M, Esmaeil N, Maracy MR, Hoorfar H, Jalaeikar M. A randomized double-blind, placebo-controlled study of therapeutic effects of silymarin in β-thalassemia major patients receiving desferrioxamine. *Eur J Haematol* 2013, 90(3):202-209

Morelli I. Costituenti del Silybum marianum e loro impiego in terapia. *Boll Chim Farm* 1978, 117:258-267

Mourelle M, Franco MT. Erythrocyte defects precede the onset of CCl4-induced liver cirrhosis. Protection by silymarin. *Life Sci* 1991, 48(11):1083-1090

Mourelle M, Favari L, Amezcua JL. Protection against thallium hepatotoxicity by silymarin. *J Appl Toxicol* 1988, 8(5):351-354

Münter K, Mayer D, Faulstich H. Characterization of a transporting system in rat hepatocytes. Studies with competitive and non-competitive inhibitors of phalloidin transport. *Biochim Biophys Acta* 1986, 860:91-98

Muriel P, Moreno MG. Effects of silymarin and vitamins E and C on liver damage induced by prolonged biliary obstruction in the rat. *Basic Clin Pharmacol Toxicol* 2004, 94:99-104

Muriel P, Mourelle M. Prevention by silymarin of membrane alterations in acute CCl4 liver damage. *J Appl Toxicol* 1990, 10:275-279

Muriel P, Garciapina T, Perez-Alvarez V, Mourelle M. Silymarin protects against paracetamol-induced lipid peroxidation and liver damage. *J Appl Toxicol* 1992, 12(6):439-442

Müzes G, Deak G, Lang I, Nekam K, Niederland V, Feher J *et al*. Effect of silimarin (Legalon) therapy on the antioxidant defense mechanism and lipid peroxidation in alcoholic liver disease (double blind protocol). *Orvosi hetilap* 1990, 131(16):863-866

Nassuato G, Iemmolo R, Strazzabosco M, Lirussi F, Deana R, Francesconi MA, *et al*. Effect of Silibinin on biliary lipid composition experimental and clinical study. *J Hepatol* 1991, 12:290-295

Navarro C, Montilla P. Interés terapéutico del fruto cardo mariano. Revista de Fitoterapia 2012, 12(2): 101-116

Palasciano G, Portincasa P, Palmier V, *et al*. The effect of silymarin on plasma levels of malondialdehyde in patients receiving long-term treatment with psychotropic drugs. *Curr Ther Res Clin Exp* 1994, 55:537-545

Pandey GP, Srivastava DN. Phytochemical and acute toxiticy studies of *Silybum marianum* and *Wedelia calendulacea*. *Indian Vet J* 1990, 67(8):773-776

Pares A, Planas R, Torres M, Caballería J, Viver JM, Acero D, *et al*. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. *J Hepatol* 1998, 28:615-621

PDR for Herbal Medicines, 1st ed. Gruenwald J, Jaenicke C and Brendler T, editors. Physicians Desk Reference Inc. 1998

Petronelli A, Roda E, Briganti M, Morselli Labate AM, Barbara L. Effetto della somministrazione di silimarina sui livelli dei lipidi sierici. *Cl Terap.* 1981, 99:471-482

Piscitelli SC, Formentini E, Burstein AH, Alfaro R, Jagannatha S, Falloon J. Effect of milk thistle on the pharmacokinetics of indinavir in healthy volunteers. *Pharmacother* 2002, 22:551-556

Polyak SJ, Morishima C, Shuhart MC, Wang CC, Liu Y, Lee DY. Inhibition of T-cell inflammatory cytokines, hepatocyte NF-kappaβ signaling and HVC infection by standardized Silymarin. *Gastroenterology* 2007, 132:1925-1936

Polyak SJ, Morishima CH, Lohmann V, Pal S, Lee DYW, Liu Y, *et al*. Identification of hepatoprotective flavonolignans from silymarin. PNAS 2010, 107:5995-5999

Poser G. Erfahrungen mit Silymarin bei der Behandlung chronischer Lebererkrankungen. *Arzneim Forsch Drug Res.* 1971, 21(8):1209-1212

Potter's New Cyclopaedia of Botanical Drugs and Preparations (1988, 2003)

Pradhan SC, Girish C. Hepatoprotective herbal drug, silymarin from experimental pharmacology to clinical medicine. Indian J Med Res 2006, 124:491-504

Public statement on the interpretation of therapeutic indications appropriate to traditional herbal medicinal products in Community herbal monographs, EMA/HMPC/473587/2011, 13 September

Quercia V, Pierini N, Incarnato G, Terracciano M, Papetti P. Identification and assay by HPLC of the flavonoid components of *Silybum marianum* in medicinal specialities. *Fitoterapia* 1980, 51(2):83-88

Rambaldi A, Jacobs BP, Iaquinto G, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C liver diseases – a systematic Cochrane hepato-biliary group. Review with meta-analyses of randomized clinical trials. *Am J Gastroenterol* 2005, 100:2583-2591

Rambaldi A, Jacobs BP, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. Cochrane Database of Systematic Reviews 2008, Issue 2. Chichester, UK: John Wiley & Sons, Ltd.Art. No.: CD003620. DOI: 10.1002/14651858.CD003620.pub3

Rao BN, Srinivas M, Kumar YS, Rao YM. Effect of silymarin on the oral bioavailability of ranitidine in healthy human volunteers. *Drug Metabol and Drug Interac* 2007, 22(2-3):175-185

Realini S, Gonvers JJ, Hofstetter JR. Essai clinique de la silymarine dans les affections chroniques du foie. *Schweiz Rundsch Med Prax* 1975, 64:595-598

Reddy KR, Belle SH, Fried MW, Afdhal N, Navarro VJ, Hawke RL, *et al*. Rationale, challenges, and participants in a Phase II trial of a botanical product for chronic hepatitis C. *Clin Trials* 2012, 9:102–112

Saba P, Galeone F, Salvadorini F, Guarguaglini M, Troyer C. Effetti terapeutici della silimarina nelle epatopatie croniche indottet da psicofarmaci. *Gaz Med It* 1976, 135:236-251

Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. *Drugs* 2001, 61(14):2035-2063

Saller R, Melzer J, Reichling J, Brignoli R, Meier R. An updated systematic review with meta-analysis for the clinical evidence of silymarin. *Forschende Komplementärmedizin* 2006, 15(1):9-20

Saller R, Melzer J, Reichling J, Brignoli R, Meier R. An updated systematic review of the pharmacology of silymarin. *Forsch Komplementärmed* 2007, 14:70-80

Saller R, Brignoli R, Melzer J, Meier R. An Updated Systematic Review with Meta-Analysis for the Clinical Evidence of Silymarin. *Forsch Komplementärmed* 2008, 15:9–20

Salmi HA, Sarna S. Effect of silymarin on chemical, functional, and morphological alterations of the liver. *Scand J Gastroenterol* 1982, 17:517-521

Sarre H. The clinical experience regarding Silymarin in the treatment of chronic liver diseases. [in German]. *Arneimittelforschung* 1971, 21(8):1209–12

Scambia G, De Vincenzo R, Ranelletti FO, Benedetti Pancini P, Ferrandina G, D'Agostino G, *et al*., Antiproliferative effect of silybin on gynaecological malignancies: synergism with cisplatin and doxorubicin. *Eur J Cancer* 1996, 32A:877-882

Schandalik R, Gatti G, Perucca E. Pharmacokinetics of silibyn in bile following administration of silipide and silymarin in cholecystectomy patients. *Arzneimittelforschung* 1992, 42:964-968

Schrieber SJ, Wen Z, Vourvahis M, Smith PC, Fried MW, Kashuba ADM, *et al*. The pharmacokinetics of silymarin is altered in patients with hepatitis c virus and nonalcoholic fatty liver disease and correlates with plasma caspase-3/7 activity. *Drug Metabolism and Disposition* 2008, 36(9):1909–1916

Schrieber SJ, Hawke RL, Wen Z, Smith PC, Reddy KR, Wahed AS, *et al*. Differences in the disposition of silymarin between patients with nonalcoholic fatty liver disease and chronic hepatitis C. Drug Metab Dispos 2011, 39(12):2182–2190

Schuppan D, Hahn E. Clinical studies with silymarin: Fibrosis progression is the end point. *Hepatology* 2001, 33:483-484

Schuppan D, Strösser W, Burkard G, Walosek G. Legalon® lessens fibrosing activity in patients with chronic liver diseases [Verminderung der Fibrosierungsaktivität durch Legalon bei chronischen Lebererkrankungen]. *Z Allgemeinmed Med* 1998, 74:577-584

Shaker E, Mahmoud H, Mna S. Silymarin, the antioxidant component and *Silybum marianum* extracts prevent liver damage. *Food Chem Toxicol* 2010, 48:803–806

Shear NH, Malkiewicz IM, Klein D, Koren G, Randor S, Neuman MG. Acetaminophen-induced toxicity to human epidermoid cell line A431 and hepatoblastoma cell line Hep G2, in vitro, is diminished by silymarin. *Skin Pharmaco*. 1995, 8(6):279-291

Singh RP, Dhanalakshmi S, Tyagi AK, Chan DCF, Agarwal C, Agarwal R. Dietary feeding of silibinin inhibits advance human prostate carcinoma growth in athymic nude mice, and increases plasma insulin-like growth factor-binding protein-3 levels. *Cancer Res* 2002, 62:3063–3069

Smith WA, Lauren DR, Burgrss EJ, Perry NB, Martin RJ. A silychristin isomer and variation of flavonolignan levels in milk thistle (*Silybum marianum*) fruits. *Planta Med* 2005, 71:877–880

Sonnenbichler J, Zetl I. Biochemical effects of the flavonolignane silibinin on RNA protein and DNA synthesis in rat livers. *Progress in Clinical and Biological Research* 1986, 213:319-331

Sonnenbichler J, Zetl I. Biochemistry of a liver drug from the thistle *Silybum marianum*. *Planta medica* 1992, 58:580

Srivastava S, Srivastava AK, Srivastava S Patnaik GK, Dhawan BN. Effect of picroliv and silymarin on liver regeneration in rats. *Indian J Pharmacol* 1994, 26:19-22

Steele VE, Kelloff GJ, Wilkinson BP, Arnold JT. Inhibition of transformation in cultured rat tracheal epithelial cells by potential chemopreventive agents. *Cancer Res* 1990, 50(7):2068-2074

Strickland GT, Tanamly MD, Tadros F, *et al*. Two-year results of a randomized double-blinded trial evaluating silymarin for chronic hepatitis C. *Digest Liver Dis* 2005, 37:542-543

Strubelt O, Siegers CP, Younes M. The influence of silybin on the hepatotoxic and hypoglycemic effects of praseodymium and other lanthanides. *Arzneim Forsch Drug Res* 1980, 30(10):1690-1694

Sweetman S. Martindale: The Complete Drug Reference. 33rd ed. Pharmaceutical Press, London 2002

Szilard S, Szentgyorgyi O, Demeter I. Protective effect of Legalon in workers exposed to organic solvents. *Acta Med Hungarica* 1988, 45(2):249-256

Tamayo C, Diamond S. Review of clinical trials evaluating safety and efficacy of milk thistle (*Silybum marianum* (L.) Gaertn.). *Integr Cancer Ther* 2007, (6):146-157

Tanamly MD, Tadros F, Labeeb S, Makld H, Shehata M, Mikhail N, *et al*. Randomised double-blinded trial evaluating silymarin for chronic hepatitis C in an Egyptian village: study description and 12-month results. *Dig Liver Dis* 2004, 36(11):752-759

Tănăsescu C, Petrea S, Bălдescu R, Macarie E, Chiriloiu C, Purice S. Use of the Romanian product Silimarina in the treatment of chronic liver diseases. *Med Interne* 1988, 26(4):311-322

Teel RW. Effect of phytochemicals on the mutagenicity of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridil)-1-butanone (NNK) in Salmonella typhimurium strain TA 1535. *Phytotherapy Res* 1993, 7:248-251

The Merk Index. Merk & Co. Inc., Whitehouse Station, N.J., U.S.A. 1976

Thelen P, Wuttke W, Jarry H, Grzmil M, Ringert RH. Inhibition of telomerase activity and secretion of prostate specific antigen by silibinin in prostate cancer cells. *J Urology* 2004, 171:1934-1938

Trappoliere M, Caligiuri A, Schmid M, Bertolani C, Failli P, Vizzutti F, *et al*. Silybin, a component of sylimarin, exerts anti-inflammatory and anti-fibrogenic effects on human hepatic stellate cells. *J Hepatol* 2009, 50(6):1102-1111

Trinchet JC, Coste T, Levy VG, Vivet F, Duchatelle V, Legendre C, *et al*. Traitement de l´hépatite alcoolique par la silymarine. *Gastroenterol Clin Biol* 1989, 13:120-124

Tsai JH, Liu JY, Wu TT, Ho PC, Huang CY, Shyu JC, *et al*. Effects of silymarin on the resolution of liver fibrosis induced by carbon tetrachloride in rats. *J Viral Hepat* 2008, 5(7):508-514

Tyagi A, Bhatia N, Condon MS, Bosland MC, Agarwal C, Agarwal R. Antiproliferative and apoptotic effects of silibinin in rat prostate cancer cells. *Prostate* 2002, 53:211-217

Usman M, Ahmad M, Madni AU, Akhtar N, Asghar W, Akhtar M, *et al*. *In-vivo* Kinetics of Silymarin (Milk Thistle) on Healthy Male Volunteers. *Tropical Journal of Pharmaceutical Research* 2009, 8(4):311-316

Valenzuela A, Aspillaga M, Vial S, Guerra R. Selectivity of silymarin on the increase of the glutatione content in different tissues of the rat. *Planta Med* 1989, 55:420-422

van Pelt JF, Verslype C, Crabbé T, Zaman Z, Fevery J. Primary human hepatocytes are protected against prolonged and repeated exposure to ethanol by silibinin-dihemisuccinate. Alcohol Alcohol 2003, 38(5):411-414

Velussi M, Cernigoi AM, Viezzoli L, Dapas F, Caffau C, Zilli M. Silymarin reduces hyperinsulinemia, malondialdehyde levels, and daily insulin need in cirrhotic diabetic patients. *Current Ther Res* 1993, 53(5):533-545

Velussi M, Cernigoi AM, DeMonte A, Dapas F, Caffau C, Zilli M. Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need, and malondialdehyde levels in cirrhotic diabetic patients. *J Hepatol* 1997, 26(4):871–879

Vereckei A, Besch HR, Zipes DP. Combined amiodarone and silymarin treatment, but not amiodarone alone, prevents sustained atrial flutter in dogs. *Journal of Cardiovascular Electrophysiology* 2003, 14(8):861-967

Wagner H, Mohan Chari V, Seitz M, Riess-Maurer I. The structure of silychristin - a 13C-NMR study. *Tetrahedron Letters* 1978, 4:381-384

Wagner H. The antihepatotoxic principle of *Silybum marianum* Gaertn. Recent Develop. *Chem Natur Carbon Comp* 1973, 5:51-68

Wagoner J, Negash A, Kane OJ, Martinez LE, Nahmias Y, Bourne N, *et al*. Multiple effects of silymarin on the hepatitis C virus life cycle. *Hepatology* 2010, 51(6):1912-1921

Wen Z, Dumas TE, Schrieber SJ, Hawke RL, Fried MW, Smith PC. Pharmacokinetics and metabolic profile of free, conjugated, and total silymarin flavonolignans in human plasma after oral administration of milk thistle extract. *Drug Metabolism and Disposition* 2008, 36(1):65–72

Wenzel S, Stolte H, Soose M. Effects of silibinin and antioxidants on high glucose-induced alterations of fibronectin turnover in human mesangial cell cultures. *J Pharmacol Exp Ther* 1996, 279(3):1520-1526

WHO monographs on selected medicinal plants. Vol 2. Fructus Silybi Mariae. World Health Organization. Geneva 2002

Woo JS, Kim TS, Park JH, Sang-Cheol ChP. Formulation and Biopharmaceutical Evaluation of Silymarin Using SMEDDS. *Arch Pharm Res* 2007, 30(1):82-89

Wren RC. 1988. Potter's new cyclopaedia of Botanical Drugs and Preparations. Safron Walden, The C.W. Daniel Company Limited, Essex 1998

Wu CG, Chamuleau RAFM, Bosch KS, Frederiks WM. Protective effect of silymarin on rat liver injury induced by ischemia. *Virchows Archiv B Cell Pathol* 1993, 64:259-263

Zhang W, Hong R, Tian T. Silymarin's Protective Effects and Possible Mechanisms on Alcoholic Fatty Liver for Rats. *Biomol Ther (Seoul)* 2013, 21(4):264–269

Zhu HJ, Brinda BJ, Chavin KD, Bernstein HJ, Patrick KS, Markowitz JS. An assessment of pharmacokinetics and antioxidant activity of free silymarin flavonolignans in healthy volunteers: a dose escalation study. *Drug Metabolism and Disposition* 2013, 41:1679–1685

Zi X, Agarwal R. Modulation of mitogen-activated protein kinase activation and cell cycle regulators by the potent skin cancer preventive agent silymarin. *Biochem Biophys Res Comm* 1999a, 263:528-536

Zi X, Agarwal R. Silibinin decreases prostate-specific antigen with cell growth inhibition via G1 arrest, leading to differentiation of prostate carcinoma cells: Implications for prostate cancer intervention. *Proc Natl Acad Sci USA* 1999b, 96:7490-7495