



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 September 2011
EMA/HMPC/369803/2009
Committee on Herbal Medicinal Products (HMPC)

List of references supporting the assessment of *Chelidonium majus* L., herba

Final

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.

Adler M, Appel K, Canal T. Effect of *Chelidonium majus* extracts on hepatocytes *in vitro*. *Planta Medica* 2006, 72: 1077

Amoros M, Fauconnier B, Girre L. Propriétés antivirales de quelques extraits de plantes indigènes. *Annals Pharm Françaises*. 1977, 35: 371-376

Ansari K., Dhawan A., Subhash K., Khanna, Das M. Protective effect of bioantioxidants on argemone oil/sanguinarine alkaloid induced genotoxicity in mice. *Cancer Letters* 2006, 244: 109-118

Ardja H. Therapeutische Aspekte der funktionellen Oberbauchbeschwerden bei Gallenwegserkrankungen. *Fortschritte der Medizin* 1991, 109 Suppl. 115: 2-8

Barnes J, Anderson L, Phillipson D. Herbal Medicines: A Guide for Healthcare. Pharmaceutical Press, London 2007, 136-145

Basini G, Santini S, Bussolati S, Grasselli F. The Plant Alkaloid Sanguinarine is a Potential Inhibitor of Follicular Angiogenesis. *Journal of Reproduction and Development* 2007, 53(3): 573-579

BfArM. Bekanntmachung zur Abwehr von Gefahren durch Arzneimittel, Stufe II, Entscheidung (here: ‚Schöllkraut-haltige Arzneimittel zur innerlichen Anwendung‘). 9 April 2008

Bichler B. Fallbericht aus der Praxis: Hepatitis unklarer Genese. *Phytotherapie* 2009, 6: 19-20

Boegge SC, Kesper S, Verspohl EJ, Nahrstedt A. Reduction of ACh-induced contraction of rat isolated ileum by coptisine, (+)-caffeoylmalic acid, *Chelidonium majus*, and *Corydalis lutea* extracts. *Planta Medica* 1996, 62(2): 173-4

Benninger J, Schneider HT, Schuppan D, Kirchner T, Hahn EG. Acute hepatitis induced by greater celandine (*Chelidonium majus*). *Gastroenterology* 1999, 117: 1234-1237



Blumenthal M, Busse W, Goldberg A, Gruenwald J, Hall T, Riggins C, Rister R. The complete German commission E Monographs: Therapeutic guide to herbal medicines. American Botanical Council. Austin, Texas 1998, 105-106

Boulware RT, Southard GL, Yankell SL. Sanguinaria extract, a new agent for the control of volatile sulphur compounds in the oral cavity. *Journal of the Society of Cosmetic Chemists* 1985, 36(4): 297-302

Bruneton J. Pharmacognosie en fytochimie: plantes médicinales. 3rd ed. TEC et DOC, Lavoisier, Paris 1999, 917

Caolo MA, Stermitz FR. Benzophenanthridinium salt equilibria. *Heterocycles* 1979, 12(1): 11-5

Chen CM, Chang HC. Determination of berberine in plasma, urine and bile by high-performance liquid chromatography. *Journal of Chromatography B* 1995, 665: 117-123

Chung HS, An HJ, Jeong HJ, Won JH, Hong SH, Kim HM. Water extract isolated from *Chelidonium majus* enhances nitric oxide and tumour necrosis factor- α production via nuclear factor- κ B activation in mouse peritoneal macrophages. *Journal of Pharmacy and Pharmacology* 2004, 56(1): 129-34

Crijns APG, De SMet PAGM, Van den Heuvel M, Schot BW, Haagsma EB. Acute hepatitis na gebruik van een plantaardig preparaat met stinkende gouwe (*Chelidonium majus*). *Ned Tijdschr Geneesk* 2002, 146(3): 124-127

Dalvi RR. Sanguinarine: its potential as a liver toxic alkaloid present in the seeds of *Agremone mexicana*. *Experientia* 1985, 41: 77-78

Debiton E, Madelmont JC, Legault J, Barthomeuf C. Sanguinarine induced apoptosis is associated with an early and severe glutathione depletion. *Cancer Chemother Pharmacol* 2003, 51: 474-482

Delfosse M. drogues végétales et plantes medicinales. APB, Brussels 1998, 131-132

Dvorak Z, Sovadinova I, Blaha L, Giesy J, Ulrichova J. Quaternary benzo [c]phenanthridine alkaloids sanguinarine and chelerythrine do not affect transcriptional activity of aryl hydrocarbon receptor: Analyses in rat hepatoma cell line H4IIE.luc. *Food and Chemical Toxicology* 2006, 44: 1466-1473

ESCOP Monographs 2nd ed. European Scientific Cooperative on Phytotherapy, editor. Thieme, Stuttgart 2003, 74-78

Etxenagusia MA, Anda M, Gonzalez-Mahave I, Fernandez E, Fernandez de Corres L. Contact dermatitis from *Chelidonium Majus* (greater celandine). *Contact Dermatitis* 2000, 43: 47

European Pharmacopoeia 6th ed. Vol. 2. Council of Europe. 01/2008: 1861

Faddejeva MD, Belyaeva TN, Rosanov YM, Sedova VM, Sokolovskaya EL. Studies on the complex-formation with DNA and the effect on DNA hydrolysis, RNA-synthesis and cellular membrane ATPase systems of some antitumoragents including alkaloids. *Studia Biophysica* 1984, 104(1-3): 267-9

Fik E *et al.* new plant glycoprotein against methicillin resistant *Staphylococci* and *Enterococci*. *Acta microbiologica polonica* 1997, 46: 325-327

Frankos VH, Brusick DJ, Johnson EM *et al.* Safety of sanguinaria extract as used in commercial toothpaste and oral rinse products. *J Can Dent Associat* 1990, 56(7): 41-47

Garcia-Cortes M, Lucena MI, Pachkoria K, *et al.* Evaluation of Naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. *Aliment Pharmacol Ther* 2008, 27: 780-789

- Granger I, Serradeilleg C, Augereau JM, Gleye J. Benzophenanthridine alkaloids isolated from *eschscholtzia californica* cell suspension cultures interact with Vasopressin (V1) receptors. *Planta Medica*, 58(1): 35-8
- Gutsche H. Langzeitbehandlung mit einem Phytochologogum. *Ärztliche Praxis* 1977, 29 (98): 399-400
- Haddouk H. Bacterial reverse mutation test. Weleda 2001
- Häberlein H *et al.* *Chelidonium majus* L.: components with in vitro affinity for the GABA_A receptor. Positive cooperation of alkaloids. *Planta Med* 1996, 62: 227-231
- Hänsel R, Keller K, Rimpler H, Schneider G, editors. Hagers Handbuch der Pharmazeutischen Praxis. 5th ed. Springer Verlag, Berlin 1992
- Hardeman E, Van Overbeke L, Ilegems S, Ferrante M. Acute hepatitis induced by greater celandine (*Chelidonium majus*). *Acta Gastro-Enterologica* 2008, 71(2): 281-2
- Hiller KO, Ghorbani M, Schilcher H. Antispasmodic and relaxant activity of chelidonine, protopine, coptisine, and *Chelidonium majus* extracts on isolated guinea-pig ileum. *Planta Medica* 1998, 64(8): 758-60
- Hladon B *et al.* Cytotoxic activity of some *Chelidonium majus* alkaloids on human and animal tumor cell cultures in vitro. *Ann Pharm (Poznan)* 1978, 13: 61-8
- Ishii H, Ichikawa Y, Kawanabe E, Ishikawa M, Ishikawa T, Kuretani K, Inomata M and Hoshi A. Studies on the chemical constituents of rutaceous plants. LX. Development of a versatile method for Syntheses of the antitumor benzophenanthridine alkaloids. Efficient syntheses and antitumour activities of Nitidine and related nonphenolic benzophenanthridine alkaloids. *Chem Pharm Bull* 1985, 33: 4139-51
- Kaminsky V, Lin KW, Filyak Y, Stoika R. Differential effect of sanguinarine, chelerythrine and chelidonine on DNA damage and cell viability in primary mouse spleen cells and mouse leukemic cells. *Cell Biology International* 2007, 32: 271-277
- Kardos J, Blasko G, Simonyi M. Enhancement of gamma-aminobutyric acid receptor binding by protopine-type alkaloids. *Arzneimittel-Forschung/Drug Research* 1986, 36(6): 939-40
- Kelber O, Wittwer A, Lapke C, Kroll U, Weiser D, Okpanyi SN, Heilmann J. Ex vivo/in vitro absorption of STW 5 (Iberogast) and its extract components. *Phytomedicine* 2006, 13 Suppl 5: 107-13
- Kéry A *et al.*, Antiviral alkaloid in *Chelidonium majus* L. *Acta Pharm Hung* 1987, 57: 19-25
- Kim Y, Shin M, Chung J, Kim E, Koo G, Lee C, Kim C. Modulation of *Chelidonium herba* on GABA activated chloride current in rat PAG neurons. *Am J Chin Med* 2001, 29: 265-279
- Kim DJ, Ahn B, Han BS, Tsuda H. Potential preventive effects of *Chelidonium majus* L (Papaveraceae) herb extract on glandular stomach tumor development in rats treated with N-methyl-N'-nitro-N nitrosoguanidine (MNNG) and hypertonic sodium chloride. *Cancer Letters* 1997, 112(2): 203-8
- Kim HK, Farnsworth NR, Blomster RN, Fong HHS. Biological and phytochemical evaluation of plants. V. Isolation of two cytotoxic alkaloids from *Chelidonium majus*. *Journal of Pharmaceutical Sciences* 1969, 58(3): 372
- Kniebel R, Urlacher W. Therapie krampfartiger Abdominalschmerzen. *Zeitschrift für Allgemeinmedizin* 1993, 69(25): 680-684
- Knöpfel SA. Auch gegen Gallenleiden ist ein Kraut gewachsen. *Therapeutikon* 1991, 205-208

- Kosina P, Walterova D, Ulrichova J, Lichnovsky V, Stiborova M, Rydlova H, Vicar J, Krecman V, Brabec M, Simanek V. Sanguinarine and chelerythrine: assessment of safety on pigs in ninety days feeding experiment. *Food and Chemical Toxicology* 2004, 42: 85-91
- Krey AK, Hahn FE. Berberine – complex with DNA. *Science* 1969, 166(3906): 755
- Leclerc H. Précis de phytothérapie: essais de thérapeutique par les plantes francaises, editor. Masson, 1954, 268-270
- Lenfeld J, Kroutil M, Marsalek E, Slavik J, Preininger V, Simanek V. Isolation, chemistry and biology of alkaloids from plants of the papaveraceae: anti-inflammatory activity of quaternary benzophenantrhridine alkaloids from *Chelidonium majus*. *Planta Medica* 1981, 43(2): 161-5
- Li HL, Zhang WD, Zhang C, Liu RH, Wang XW, Wang XL, Zhu JB, Chen CL. Bioavailability and pharmacokinetics of four active alkaloids of traditional Chinese medicine Yanhuanglian in rats following intravenous and oral administration. *Journal of Pharmaceutical and Biomedical Analysis* 2006, 41: 1342-1346
- Lorkowski. Clinical efficacy and tolerability of celandine containing medicines. Expert report (2011)
- Lozyuk LV, Antiviral properties of some compounds of plant origin. *Mikrobiologicheskii zhurnal* 1977, 39: 343-348
- Ma WG, Fukushi Y, Tahara S, Osawa T. Fungitoxic alkaloids from Hokkaido Papaveraceae. *Fitoterapia* 2000, 71(5): 527-34
- Mahajan VM. Et al, Antimycotic activity of Berberine sulphate: an alkaloid from an Indian medicinal herb. *Sabouraudia* 1982, 20: 79-81
- Maiti M, Nandi R, Chaudhuri K. Sanguinarine – a monofunctional intercalating alkaloid *Febs Letters* 1982, 142(2): 280-4
- Malikova J, Zdarilova A, Hlobilkova A. Effects of sanguinarine and chelerythrine on the cell cycle and apoptosis. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2006, 150(1): 5-12
- Matos OC, Baeta J, Silva MJ, Ricardo CPP. Sensitivity of Fusarium strains to *Chelidonium majus* L. extracts. *Journal of Ethnopharmacology* 1999, 66(2): 151-8
- Mazzanti G, Di Sotto A, Franchitto A et al. *Chelidonium majus* is not hepatotoxic in Wistar rats, in a 4 weeks feeding experiment. *Ethnopharmacol* 2009, 126: 518-24
- Mheddhibi, S. Four week toxicity study by oral route in rats. Weleda 2002
- Mitscher LA, Park YH, Clark D, Clark GW 3rd, Hammesfahr PD, Wu WN, Beal JL. Antimicrobial agents from higher plants. An investigation of *Hunnemannia fumariaefolia* pseudoalcoholates of sanguinarine and chelerythrine. *Lloydia* 1978, 41: 145-149
- Miyazaki H, Shirai E, Ishibashi M, Nyizima K. Quantitative analysis of berberin in urine samples by chemical ionisation mass fragmentography. *J Chromatography* 1978, 152: 79-86
- Moffat AC, Osselton MD, Widdop B, Galichet LY. Clarke's Analysis of drugs and poisons. The Pharmaceutical Press, London 2004, 692-693
- Moro PA, Cassetti F, Giugliano G, Falce M, Mazzanti G, Mennitti-Ippolito F, Raschetti R, Santuccio CJ. Hepatitis from Greater celandine (*Chelidonium majus* L.): review of literature and report of a new case. *Ethnopharmacology* 2009, 124: 328-332

- Neuman-Mangold P. Erfahrungen bei der Behandlung von Gallengangserkrankungen mit Panchelidon. *Med Welt* 1977, 28(4): 181-185
- Niederau C, Göpfert E. Die Wirkung von Schollkraut- und Kurkumawurzelstock Extrakt auf Oberbauchbeschwerden infolge funktionellen Störungen des ableitenden Gallensystems. *Medizinische Klinik* 1999, 94: 425-430
- Pascolo L, Delfino R, Bortoluzzi S. Study report 2005
- Pitea M. and Margineanu C. Correlations between chemical structure and antibacterial activity of berberine. *Clujul med* 1972, 45: 465-9
- Psotova J, Klejdus B, Vecera R, Kosina P, Kuban V, Vicar J, Simanek V, Ulrichova J A liquid chromatographic-mass spectrometric evidence of dihydrosanguinarine as a first metabolite of sanguinarine transformation in rat, *Journal of Chromatography B* 2006, 830: 165–172
- Ritter R *et al.* Clinical trial on standardised celandine extract in patients with functional epigastric complaints: results of a placebo-controlled double-blind trial. *Complement Ther Med* 1993, 1: 189-193
- Rogelj B, Popovic T, Ritonja A, Strukelj B, Brzin J. Chelidocystatin, a novel phytocystatin from *Chelidonium majus*. *Phytochemistry* 1998, 49(6): 1645-9
- Runge D, Rudolf H, Ullrich A, Ludwig K. Hepatotoxic assessment of *Chelidonium majus* L. and its alkaloids in primary hepatocyte cultures of different species. *Zeitschrift für Phytotherapie* 2009 30(1)
- Saglam H, Arar G. Cytotoxic activity and quality control determinations on *Chelidonium majus*. *Fitoterapia* 2003, 74: 127-129
- Schemann M, Michel K, Zeller F, Hohenester B, Rühl A. Region-specific effects of STW (Iberogast®) and its components in gastric fundus, corpus and antrum. *Phytomedicine* 2006, 13: 90-99
- Schmidt M. Comments on the Public Statement on *Chelidonium majus* L. *Herba*. Expert report, 2011
- Schrenk D. Statement on the toxicology of *Chelidonium majus* extracts. Expert opinion, 2011
- Sethi ML. Enzyme inhibition VI: Inhibition of reverse transcriptase activity by protoberberine alkaloids and structure-activity relationships. *Journal of Pharmaceutical Sciences* 1983, 72(5): 538-41
- Sethi ML. Screening of benzophenanthridine alkaloids for their inhibition of reverse-transcriptase activity and preliminary report on the structure activity relationships. *Canadian Journal of Pharmaceutical Sciences* 1981, 16(1): 29-34
- Sethi ML. Enzyme inhibition VII: Comparison of inhibition of reverse transcriptase and antileukemic activities exhibited by protoberberine and benzophenanthridine alkaloids and structure activity relationships. *Phytochemistry* 1985, 24(3): 447-54
- Shin MC. Modulation of *Chelidonium herba* on glycine-activated and glutamate-activated chloride current in rat PAG neurons. *Clin chim acta* 2002, 337: 93-101
- Sibaev A, Yucece B, Kelber O, *et al.* STW 5 (Iberogast®) and its individual herbal components modulate intestinal electrophysiology of mice. *Phytomedicine* 2006, 13: 80-89
- Simmen U, Kelber O, Okpanyi SM, Jäggi R, Buter B, Weiser D. Binding of STW 5 (Iberogast®) and its components to intestinal 5-HT, muscarinic M3, and opioid receptors. *Phytomedicine* 2006, 13: 51–55
- Smekal E, Kubova N, Kleinwachter V. DNA – chelerythrine interaction and binding isotherms. *Studia Biophysica* 1985, 105(2): 77-84

- Smekal E, Kubova N, Kleinwachter V. interaction of benzophenanthridien alkaloid sanguinarine with DNA. *Studia Biophysica* 1984, 101: 125-32
- Smekal E, Kubova N. alkaloids of protoberberinen and benzophenanthridine groups as intercalating drugs with DNA. *Studia Biophysica* 1984, 101: 121-3
- Sokoloff B. oncostatic and oncolytic factors present in certain plants. *Oncology* 1968,; 22(1): 49
- Sokoloff B, Saelhoff CC, Takeushi Y, Powella R. The antitumor factors present in *Chelidonium majus* L. I. Chelidonine and protopine. *Growth* 1964, 28: 225-231
- Song JY, Yang HO, Pyo SN, Jung IS, Yi SY, Yun YS. Immunomodulatory activity of protein-bound polysaccharide extracted from *Chelidonium majus*. *Archives of Pharmacal Research* 2002, 25(2):158-64
- Song JY, Yang HO, Shim JY, et al. Radiation protective effect of an extract from *Chelidonium majus*. *International Journal of Hematology* 2003, 78(3): 226-32
- Southard G *et al.* Benzophenanthridine alkaloids containing solutions for treating periodontal diseases. U.S. US 4683133, 1987
- Stiborová M, Šimánek V, Frei E, Hobza P, Ulrichová J. DNA adduct formation from quaternary benzo[c]phenanthridine alkaloids sanguinarine and chelerythrine as revealed by the 32P-postlabeling technique. *Chem Biol Interact* 2002, 140(3): 231-42
- Stiborova M, Vostalova J, Zdarilova A, Ulrichova J, Hudecek J, Tschirner K, Simanel V. Macleaya cordata extract and Sangrovit® genotoxicity assessment in vivo. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2008, 152 (1): 35-39
- Stickel F, Seitz HK, Hahn EG, Schuppan D. Hepatotoxizität von Arzneimittel pflanzlichen Ursprungs. *Z Gastroenterol* 2001, 39: 225-237
- Tan GT, Pezzuto JM, Kinghorn AD, Hughes SH. Evaluation of natural products as inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase. *J Nat Prod* 1991, 54: 143-154
- Ulrichová J, Walterová D, Vavrečková C, Kamarád V, Šimánek V. Cytotoxicity of Benzo[c]phenanthridinium Alkaloids in Isolated Rat Hepatocytes. *Phytother Res* 1996, 10: 220-223
- Ulrichova J, Dvorak Z, Vicar J, Lata J, Smrzova J, Sedo A, Simanek V. Cytotoxicity of natural compounds in hepatocyte cell culture models. *Toxicological letter* 2001, 125: 125-132
- Vahlensieck U *et al.* The effect of *Chelidonium majus* herb extract on choleresis in the isolated perfused rat liver. *Plant med* 1995, 61: 267-270
- Van Hellemont J. Fytotherapeutisch compendium, Belgian Pharmaceutical Society, Brussels, 144-146
- Vavreckova C, Gawlik I, Muller K. Benzophenanthridine alkaloids of *Chelidonium majus* I: Inhibition of 5- and 12-lipoxygenase by a non-redox mechanism. *Planta Medica* 1996a, 62(5): 397-401
- Vavreckova C, Gawlik I, Muller K. Benzophenanthridine alkaloids of *Chelidonium majus* II: Potent inhibitory action against the growth of human keratinocytes. *Planta Medica* 1996b, 62(6): 491-4
- Wegener T, Wagner H. The active components and the pharmacological multi-target principle of STW5 (Iberogast). *Phytomedicine* 2006, 13: 20-35
- Weiss RF, Fintelman V, Lehrbuch der Phytotherapie, Hippocrates Verlag, Stuttgart 1999, 131-132

Zdarilova A, Vrzal R, Rypka M, Ulrichova J, Dvorak Z. Investigation of sanguinarine and chelerythrine effects on CYP1A1 expression and activity in human hepatoma cells. *Food and Chemical Toxicology* 2006, 44: 242–249

Zhu B, Ahrens FA. Effect of Berberine on intestinal secretion mediated by *Escherichia-coli* heat stable enterotoxin in jejunum of pigs. *American Journal of Veterinary Research* 1982, 43(9): 1594-8

Zuo GY, Meng FY, Hao XY, Zhang YL, Wang GC, Xu GL. Antibacterial Alkaloids from *Chelidonium majus* Linn (Papaveracea) against clinical isolates of methicillin-resistant *Staphylococcus aureus*. *J Pharm Pharmaceut Sci* 2008, 11(4): 90-94

References not included in the Assessment report

Capasso F, Gaginella T, Lieb E. *Phytotherapie: A quick reference to herbal medicine*. Springer Verlag Berlin, Heidelberg, New York 2003, 307

Cohen HG, Seifen EE, Straub KD, Tiefenback C, Stermitz FR. Structural specificity of NaK ATPase inhibition by sanguinarine, an isoquinoline benzophenanthridine alkaloid. *Biochemical Pharmacology* 1978, 27(21): 2555-8

Colombo ML, Bosisio E. Pharmacological activities of *Chelidonium majus* L (Papaveraceae). *Pharmacological Research*. 1996 Feb, 33(2): 127-34

Gansauge F, Ramadani M, Pressmar J, Gansauge S, Muehling B, Stecker K, Cammerer G, Leder G, Beger H. NSC-631570 (Ukrain) in the palliative treatment of pancreatic cancer: results of a phase II trial. *Langenbeck's Arch Surg* 2002, 386: 570-574, Professionals, Pharmaceutical press

Horvath J *et al.* Antiviral effect of *Chelidonium* extracts. *Proc Int Congr Chemother* 13th ed. 1983, 9(124): 106-110

Kelber O, Wittwer A, Lapke C, Kroll U, Weiser D, Okpanyi SN, Heilmann J. Ex vivo/in vitro absorption of STW 5 (Iberogast) and its extract components. *Phytomedicine* 2006, 13: 107-113

Kokoska L, Polesny Z, Rada V, Nepovim A, Vanek T. Screening of some Siberian medicinal plants for antimicrobial activity. *Journal of Ethnopharmacology* 2002, 82(1): 51-53

Mackraj I, Govender T, Gathiram P. Sanguinarine. *Cardiovascular Therapeutics* 2008, 26: 75–83

Madisch A *et al.* Ein phytotherapeutikum und seine modifizierte rezeptur bei funktioneller dyspepsie. Ergebnisse einer doppelblinden plazebokontrollierten vergleichstudie. *Z Gastroenterol* 2001 39: 511-517

Niu C *et al.*, Review of the studies on *Chelidonium majus* L. *Zhongguo Yaoxue Zazhi* 1994, 29: 138-140

Sárközi A, Then M, Szentmihályi K, (2005) *Acta Alimentaria* 34, 113-120

Stickel F, Schuppan D. Herbal medicine in the treatment of liver diseases. *Digestive and Liver Disease* 2007; 39: 293-304

Tomè F, Colombo M. Distribution of alkaloids in *Chelidonium majus* and factors affecting their accumulation. *Phytochemistry* 1995; Vol. 40, No. 1: 37-39

Tsurui Yakuhin Kogyo KK. Anticaries agents. Jpn. Kokai tokkyo JP 82 85319, 1982