

22 November 2016
EMA/HMPC/759584/2015
Committee on Herbal Medicinal Products (HMPC)

List of references supporting the assessment of *Aloe barbadensis* Mill. and *Aloe* (various species, mainly *Aloe ferox* Mill. and its hybrids), folii succus siccatus

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.

Akao T, Che QM, Kobashi K, Hattori M, Namba T. A purgative action of barbaloin is induced by Eubacterium sp. strain BAR, a human intestinal anaerobe, capable of transforming barbaloin to aloe-emodin anthrone. *Biological & Pharmaceutical Bulletin* 1996, 19(1):136–138

Anliker MD, Itin P, Wüthrich B. Anaphylactic shock due to the local application of Aloe vera leaves. *Allergy* 2002, 57:311

Ashafa AOT, Sunmonu TO, Abass AA, Ogbe AA. Laxative potential of the ethanolic leaf extract of Aloe vera(L.) Burm. f. in Wistar rats with loperamide-induced constipation. *Journal of Natural Pharmaceuticals* 2011, 2(3):158

BAnz Nr 133, 21.7.1993: German monograph Kommission E on Aloe, Bundesanzeiger No. 133, 21 July 1993

Barrantes E, Guinea M. Inhibition of collagenase and metalloproteinases by aloins and aloe gel. *Life Sci.* 2003, 72(7):843-850

Berkelhammer C, Ekambaram A, Silva RG. Low-volume oral colonoscopy bowel preparation: sodium phosphate and magnesium citrate. *Gastrointest Endosc* 2002, 56(1):89-94

Beuers U, Spengler U, Pape GR. Hepatitis after chronic abuse of senna. *Lancet* (England) 1991, 337(8737):372-373

Beya W, Davidson B, Erlwanger KH. The effects of crude aqueous and alcohol extracts of Aloe vera on growth and abdominal viscera of suckling rats. *Afr J Tradit Complement Altern Med.* 2012, 9(4):553-560. E-Collection 2012

- Blaschek W, Ebel S, Hackenthal E, Holzgrabe U, Keller K *et al.*, editors. HagerROM 2003: Hagers Handbuch der Drogen und Arzneistoffe. Version 3.0. Aloe barbadensis (Curaçao-Aloe). Aloe capensis (Kap-Aloe). Springer Verlag, Heidelberg 2003
- Blaschek W, Ebel S, Hackenthal E, Holzgrabe U, Keller K *et al.*, editors. HagerROM 2003: Hagers Handbuch der Drogen und Arzneistoffe. Version 3.0. Sokotra-Aloe. Springer Verlag, Heidelberg 2003
- Boudreau MD, Beland FA, Nichols JA, Pogribna M. Toxicology and carcinogenesis studies of a nondecolorized [corrected] whole leaf extract of Aloe barbadensis Miller (Aloe vera) in F344/N rats and B6C3F1 mice (drinking water study). *Natl Toxicol Program Tech Rep Ser.* 2013, (577):1-266 Erratum in: *Natl Toxicol Program Tech Rep Ser.* 2013; (577):1
- Boudreau MD, Mellick PW, Olson GR, Felton RP, Thorn BT, Beland FA. Clear evidence of carcinogenic activity by a whole-leaf extract of Aloe barbadensis miller (aloe vera) in F344/N rats. *Toxicol Sci.* 2013, 131(1):26-39
- British Herbal Compendium, 1992, Vol 1
- British Herbal Pharmacopeia, 1990, Vol 1
- Brown JP, Dietrich PS. Mutagenicity of anthraquinone and benzanthrone derivatives in the salmonella/microsome test: activation of anthraquinone glycosides by enzymic extracts of rat cecal bacteria. *Mutation Research* 1979, 66(1):9-24
- Brusick DJ. Assessment of the genotoxic risk from laxative products containing aloe-emodin with special emphasis on aloe preparation. March 1994; unpublished
- Bundesinstitut für Arzneimittel und Medizinprodukte. Bekanntmachung über die Zulassung und Registrierung von Arzneimitteln – Abwehr von Arzneimittelrisiken, Stufe II – Humanarzneimitteln zur innerlichen Anwendung, ausgenommen nach HAB 1 hergestellte homöopathische Arzneimittel, welche Drogen, Drogenzubereitungen oder isolierte Inhaltsstoffe der Anthranoid - (Hydroxyanthracenderivat) haltigen Pflanzengattungen Andira, Cassia, Rhamnus, Rheum oder Aloe enthalten (German pharmacovigilance actions for anthranoid-containing laxatives) vom 21. Juni 1996, Bundesanzeiger vom 05.07.1996; Nr. 123:7581
- Capasso F, Mascolo N, Autore G, Duraccio MR. Effect of indomethacin on aloin and 1,8 dioxianthraquinone-induced production of prostaglandins in rat isolated colon. *Prostaglandins* 1983, 26(4):557-562
- Che QM, Akao T, Hattori M, Kobashi K, Namba T. Isolation of a human intestinal bacterium capable of transforming barbaloin to aloe-emodin anthrone. *Planta Medica* 1991, 57(1):15-19
- Chen HC, Hsieh WT, Chang WC, Chung JG. Aloe-emodin induced in vitro G2/M arrest of cell cycle in human promyelocytic leukaemia HL-60 cells. *Food and Chemical Toxicology* 2004, 42(8):1251–1257
- Chung JH, Cheong JC, Park KS, Roh HK, Cha YN. Effect of aloin, a quinone derivative of aloe, on ethanol metabolism in the rat. *Medical Science Research* 1996, 24(6):421–423
- Cooke WT. Laxative abuse. *Acta Gastroenterol Belg.* 1981, 44(9-10):448-458
- Cruz-Caudillo JC, Sabatini S. Diabetic hyperosmolar syndrome. *Nephron* 1995, 69:201–210
- Culbreth DMR editor. A Manual of Materia Medica and Pharmacology. Aloes. 7th ed. Lea and Febiger, Philadelphia 1927

- De Witte P, Lemli J. Metabolism of ¹⁴C-rhein and ¹⁴C-rhein anthrone in rats. *Pharmacology* 1988, 36(1):152-157
- Dioscurides: Materia medica, 50-70 A.D. Aloe. Übersetzung von Julius Berendes. 3. Buch Cap. 22. 1902
- Directive 2003/36/EC of the European Parliament and of the Council of 26 May 2003
- Ennis ED, Stahl EJVB, Kreisberg RA. The hyperosmolar hyperglycemic syndrome. *Diabetes Rev* 1994, 2:115–126
- Ernst E. Adverse effects of herbal drugs in dermatology. *British Journal of Dermatology* 2000, 143(5):923-929
- ESCOP Monographs 2nd ed. Aloe capensis (Cape Aloes). European Scientific Cooperative on Phytotherapy, editor. Thieme, Stuttgart, New York, 2003, 26-31
- EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE). Phthalate migration from soft PVC toys and child-care articles: Opinion expressed at the CSTEE third plenary meeting Brussels, 24 April 1998
- Ewe K. Obstipation und Laxanzien. *Deutsche Apotheker Zeitung* 1994, 134(10):825–833 [German]
- Faber P, Strenge-Hesse A. Relevance of rhein excretion into breast milk. *Pharmacology* 1988, 36(1):212-220
- Fenig E, Nordenberg J, Beery E, Sulkes J, Wassermann L. Combined effect of aloe-emodin and chemotherapeutic agents on the proliferation of an adherent variant cell line of Merkel cell carcinoma. *Oncology reports* 2004, 11(1):213–217
- Fioramonti J, Staumont G, Garcia-Villar R, Buéno L. Effect of sennosides on colon motility in dogs. *Pharmacology*. 1988, 36 (Suppl 1):23-30
- Frerichs G, Arends G, Zörnig H, editors. Hagers Handbuch der Pharmazeutischen Praxis. Aloe. Julius Springer Verlag, Berlin 1925, 347-357
- Gabler F. Obstipation und Laxanzien. *PTA heute* 1994, 8(5):380-388 [German]
- Garcia-Villar R. Evaluation of the effects of sennosides on uterine motility in the pregnant ewe. *Pharmacology*. 1988, 36 (Suppl 1):203-211
- Ghannam N, Kingston M, Al-Meshaal IA, Tariq M, Parman NS, Woodhouse N. The antidiabetic activity of aloes: preliminary clinical and experimental observations. *Horm Res*. 1986, 24(4):288-294
- Gosmanov AR, Gosmanova EO, Dillard-Cannon E. Management of adult diabetic ketoacidosis. *Diabetes. Metab Syndr Obes*. 2014, 7:255–264
- Grimaudo S, Tolomeo M, Gancitano RA, D´Alessandro N, Aiello E. Effects of highly purified anthraquinoid compounds from Aloe vera on sensitive and multidrug resistant leukaemia cells. *Oncology Reports* 1997, 4(2):341–343
- Hattori M, Kanda T, Shu YZ, Akao T, Kobashi K, Namba T. Metabolism of barbaloin by intestinal bacteria. *Chemical and Pharmaceutical Bulletin* 1988, 36(11):4462-4466
- Haverkamp W, Haverkamp F, Breithardt G. Medikamentenbedingte QT-Verlängerung und Torsade de pointes. [Drug-induced QT Prolongation and Torsade de Pointes]. *Deutsche Ärzteblatt* 2002, 99(28-29):A1972-1979 [German]

- Heidemann A, Voelkner W, Mengs U. Genotoxicity of aloeeomod in *in vitro* and *in vivo*. *Mutation Research* 1996, 367:123-133
- Herlihy JT, Bertrand HA, Kim JD, Ikeno Y, Yu BP. Effects of *Aloe vera* ingestion in the rat. I. Growth, food and fluid intake and serum chemistry. *Phytotherapy Res.* 1998a, 12(3): 183-188
- Herlihy JT, Kim JD, Kalu DN, Nelson JF, Ward WF, Ikeno Y, Yu BP. Effects of *Aloe vera* ingestion in the rat. II. Hormonal and metabolic characteristics. *Phytotherapy Res.* 1998b, 12(3):355-360
- Hitzenberger G, Beubler E, Fleischhacker W, Fried M, Habersfeld H *et al.* Konsensuspapier Expertenforum: Obstipation und Laxanzien [Constipation and Laxatives]. *Praxis* 1999, 88:1269-1274 [German]
- Hoenig J, Geck P, RAuwald HW. Inhibition of Cl-channels as a possible base of laxative action of certain anthraquinones and anthrones. *Planta Med* 1992, 58(1):A586-A587
- Ikeno Y, Hubbard GB, Lee S, Yu BP, Herlihy JT. The influence of long-term *Aloe vera* ingestion on age-related disease in male Fischer 344 rats. *Phytotherapy Res.* 2002, 16(8):712-718
- Ishii Y, Tanizawa H, Takino Y. Studies of aloe. III. Mechanism of cathartic effect. (2). *Chemical & Pharmaceutical Bulletin* 1990, 38(1):197-200
- Ishii Y, Tanizawa H, Takino Y. Studies of aloe. IV. Mechanism of cathartic effect. (3). *Biological & Pharmaceutical Bulletin* 1994, 17(4):495-497
- Ishii Y, Tanizawa H, Takino Y. Studies of aloe. V. Mechanism of cathartic effect. (4). *Biological & Pharmaceutical Bulletin* 1994, 17(5):651-653
- Ishii Y, Takino Y, Toyooka T, Tanizawa H. Studies of aloe. VI. Cathartic effect to isobarbaloin. *Biological & Pharmaceutical Bulletin* 1998, 21(11):1226-1227
- Izzo AA, Gaginella TS, Mascolo N, Borelli F, Capasso F. NG-nitro-L-arginine methyl ester reduces senna- and cascara-induced diarrhoea and fluid secretion in the rat. *European Journal of Pharmacology* 1996, 301(1-3):137-142
- Izzo AA, Gaginella TS, Mascolo N, Capasso F. Recent findings on the mode of action of laxatives: the role of platelet activating factor and nitric oxide. *Trends in pharmacological sciences* 1998, 19(10):403-405
- Izzo AA, Sautebin L, Rombolà L, Capasso F. The role of constitutive and inducible nitric oxide synthase in senna and cascara-induced diarrhoea in the rat. *European Journal of Pharmacology* 1997, 323(1):93-97
- Izzo AA, Sautebin L, Borrelli F, Longo R, Capasso F. The role of nitric oxide in aloe-induced diarrhoea in the rat. *European Journal of Pharmacology* 1999, 368(1):43-48
- Jacobs EJ, White E. Constipation, laxative use, and colon cancer among middle-aged adults. *Epidemiology* 1998, 9(4):385-391
- Jahnke GD, Price CJ, Marr MC, Myers CB, George JD. Developmental toxicity evaluation of emodin in rats and mice. *Birth Defects Res B Dev Reprod Toxicol.* 2004, 71(2):89-101
- Japanese Pharmacopeia XV: Powdered Aloe, p 1255
- Joo JS, Ehrenpreis ED, Gonzales L, Kaye M, Breno S, Wexner SD, *et al.* Alterations in colonic anatomy induced by chronic stimulant laxatives: The cathartic colon revisited. *Journal of Clinical Gastroenterology* 1998, 26(4):283-286

- Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JL, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001, 24(1):131–153
- Koch A. Aloe als Laxans: Ein neues Argument für die Überprüfung der Droge [Aloe as a laxative: a new argument for the investigation of the drug]. *Deutsche Apotheker Zeitung* 1995, 135(12):29–32 [German]
- Kopp H. Choleretische Wirkung und Verträglichkeit von Chol-Kugeletten® bei Cholezystopathien [Choleretic effect and tolerance of a commercial formulation containing deanil benzilate, ethaverine, bisacodyl, guaiazulene, ox bile and plant extracts, in patients with gallbladder disease]. *Therapiewoche* 1979, 29(36):5645–5655 [German]
- Krumbiegel G, Schulz HU. Rhein and aloe-emodin kinetics from senna laxatives in man. *Pharmacology* 1993, 47(Suppl 1):120-124
- Kune GA, Kune S, Field B, Watson LF. The role of chronic constipation, diarrhea, and laxative use in the etiology of large-bowel cancer. Data from the Melbourne Colorectal Cancer Study. *Diseases of the colon and rectum* 1988, 31(7):507-512
- Kune GA. Laxative use not a risk for colorectal cancer: data from the Melbourne Colorectal Cancer Study. *Zeitschrift für Gastroenterologie* 1993, 31(2):140-143
- Lang W. Pharmacokinetic-metabolic studies with ¹⁴C-aloe emodin after oral administration to male and female rats. *Pharmacology* 1993, 47 (Suppl.1):110-119
- Lee A, Chui PT, Aun CST, Gin T, Lau ASC. Possible interaction between sevoflurane and *Aloe vera*. *The Annals of Pharmacotherapy* 2004, 38(10):1651-1654
- Lee HZ, Hsu SL, Liu MC, Wu CH. Effects and mechanisms of aloe-emodin on cell death in human lung squamous cell carcinoma. *European Journal of Pharmacology* 2001, 431(3):287-295
- Lee HZ, Wu CH, Chang SP. Release of nucleophosmin from the nucleus: Involvement in aloe-emodin-induced human lung non-small carcinoma cell apoptosis. *International Journal of Cancer* 2005, 113(6):971-976
- Lemli J, Lemmens L. Metabolism of sennosides and rhein in the rat. *Pharmacology* 1980, 20(1):50-57
- Liang JW, Hsiu SL, Wu PP, Chao PD. Emodin pharmacokinetics in rabbits. *Planta Med.* 1995, 61(5):406-408
- Lissoni P, Rovelli F, Brivio F, Zago R, Colciago M, Messina G, et al. A randomized study of chemotherapy versus biochemotherapy with chemotherapy plus *Aloe arborescens* in patients with metastatic cancer. *In vivo* 2009, 23(1):171-175
- Liu M, Koya S, Furuta H, Matsuzaki S. Growth-inhibiting activity of anthraquinones and benzoquinones against methicillin-resistant *Staphylococcus aureus* (MRSA). *Dokkyo Journal of Medical Sciences* 1996, 23(2):85–93
- Liu JP, Yang M, Liu Y, Wei ML, Grimsgaard S. Herbal medicines for treatment of irritable bowel syndrome (Cochrane Review). Available at: <http://www.bibliotecacochrane.com/PDF/CD004116.pdf>. Accessed 16/04/15
- Loew D, Bergmann U, Schmidt M, Ueberla KH. Anthranoidlaxanzien: Ursache für Kolonkarzinom? [Anthranoid laxatives: cause of colorectal cancer?]. *Deutsche Apotheker Zeitung* 1994, 134:30, 32–33 [German]

- Longo R. Monograph Aloe today. Part Four. *Natural 1* 2002, 74-77
- Lorenzetti LJ, Salisbury R, Beal JL, Baldwin JN. Bacteriostatic property of *Aloe vera*. *Journal of Pharmaceutical Sciences* 1964, 53:1287
- Luyckx VA, Ballantine R, Claeys M, Cuyckens F, Van den Heuvel H, Cimanga RK, *et al.* Herbal remedy-associated acute renal failure secondary to Cape aloes. *American Journal of Kidney Diseases* 2002, 39(3):E13
- Madaus G. Lehrbuch der biologischen Heilmittel 1938. Aloe. Band I. Reprint Georg Olms Verlag Hildesheim New York 1976, 484-491
- Matsuda Y, Yokohira M, Suzuki S, Hosokawa K, Yamakawa K, Zeng Y, *et al.* One-year chronic toxicity study of *Aloe arborescens* Miller var. *natalensis* Berger in Wistar Hannover rats. A pilot study. *Food Chem Toxicol.* 2008, 46(2):733-739
- Matz R. Management of the hyperosmolar hyperglycemic syndrome. *Am Fam Physician* 1999, 60:1468–1476
- Meisel JL, Bergman D, Graney D, Saunders DR, Rubin CE. Human rectal mucosa: proctoscopic and morphological changes caused by laxatives. *Gastroenterology* 1977, 72(6):1274-1279
- Mengs U. Reproductive toxicological investigations with sennosides. *Arzneimittelforschung* 1986, 36(9):1355-1358
- Mengs U, Krumbiegel G, Völkner W. Lack of emodin genotoxicity in the mouse micronucleus assay. *Mutat Res.* 1997, 393(3):289-293
- Mori H, Sugie S, Niwa K, Yoshimi N, Tanaka T, Hirono I. Carcinogenicity of chrysazin in large intestine and liver of mice. *Jpn. J. Cancer Res. (Gann)* 1986, 77:871-876
- Mori H, Sugie S, Niwa K, Takahashi M, Kawai K. Induction of intestinal tumours in rats by chrysazin. *Br J Cancer* 1985, 52:781-783
- Morimoto I, Watanabe F, Osawa T, Okitsu T, Kada T. Mutagenicity screening of crude drugs with *Bacillus subtilis* rec-assay and Salmonella/microsome reversion assay. *Mutation Research* 1982, 97(2):81-102
- Müller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. *Am J Gastroenterol* 2005, 100(1):232-242
- Müller SO, Eckert I, Lutz WK, Stopper H. Genotoxicity of the laxative drug components emodin, aloe-emodin and danthron in mammalian cells: topoisomerase II mediated? *Mutat Res.* 1996, 371(3-4):165-173
- Müller SO, Lutz WK, Stopper H. Factors affecting the genotoxic potency ranking of natural anthraquinones in mammalian cell culture systems. *Mutat Res.* 1998, 414(1-3):125-129
- Müller SO, Stopper H, Dekant W. Biotransformation of the anthraquinones emodin and chrysophanol by cytochrome P450 enzymes. Bioactivation to genotoxic metabolites. *Drug Metab Dispos.* 1998, 26(6):540-546
- Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best Pract Res Clin Gastroenterol.* 2011, 25(1):3-18
- Murakami H, Kobayashi J, Masuda T, Morooka N, Ueno Y. Omega-Hydroxyemodin, a major hepatic metabolite of emodin in various animals and its mutagenic activity. *Mutat Res.* 1987, 180(2):147-153

- Nascimbeni R, Donato F, Ghirardi M, Mariani P, Villanacci V, Salerni B. Constipation, anthranoid laxatives, melanosis coli, and colon cancer: a risk assessment using aberrant crypt foci. *Cancer Epidemiol Biomarkers Prev.* 2002, 11(8):753-757
- Nemeikaite-Ceniene A, Sergediene E, Nivinskas H, Cenas N. Cytotoxicity of natural hydroxyanthraquinones: role of oxidative stress. *Z Naturforsch C.* 2002, 57(9-10):822-827
- Nilsson SE, Takkinen S, Johansson B, Dotevall G, Melander A, Berg S, *et al.* Laxative treatment elevates plasma homocysteine: A study on a population-based Swedish sample of old people. *European Journal of Clinical Pharmacology* 2004, 60(1):45–49
- Norikura T, Kennedy DO, Nyarko AK, Kojima A, Matsui-Yuasa I. Protective effect of aloe extract against the cytotoxicity of 1,4-naphthoquinone in isolated rat hepatocytes involves modulations in cellular thiol levels. *Pharmacol Toxicol.* 2002, 90(5):278-284
- NTP Technical Report on the Toxicology and Carcinogenesis Studies of Emodin in F344/N Rats and B6C3F₁ Mice. National Toxicology Programme, June 2001, NTP TR 493, NIH Publication No. 01-3952, 1-278
- Nusko G, Schneider B, Schneider I, Wittekind C, Hahn EG. Anthranoid laxative use is not a risk factor for colorectal neoplasia: results of a prospective case control study. *Gut* 2000, 46:651-655
- Nusko G, Schneider B, Mueller G, Kusche J, Hahn EG. Retrospective study on laxative use and melanosis coli as risk factors for colorectal neo-plasma. *Pharmacology* 1993, 47(1):234-241
- Odes HS, Madar Z. A double-blind trial of a celandin, aloe vera and psyllium laxative preparation in adult patients with constipation. *Digestion* 1991, 49:65-71
- Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission related to Bis (2-ethyl) phthalate (DEHP) for use in food contact materials. Question N° EFSA-Q-2003-192, adopted on 23 June 2005 by written procedure, 1-20
- Oronzo-Barocio A, Zaitseva G, Chavez-Anaya A, Arceta-Gonzalez VI, Puebla-Perez AM *et al.* Modulation of immune response of BALB/mice bearing Lymphoma L5178Y treated with bitter yellow juice of Aloe vera (L) *in vivo.* *Russ J Immunol.* 1999, 4(1):43-50
- Park MY, Kwon HJ, Sung MK. Intestinal absorption of aloin, aloe-emodin, and aloesin; A comparative study using two in vitro absorption models. *Nutr Res Pract.* 2009, 3(1):9-14
- Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. *Diabetes Care* 2014, 37(11):3124-3131
- Pockros PJ, Foroozan P. Golytely lavage versus a standard colonoscopy preparation. Effect on normal colonic mucosal histology. *Gastroenterology* 1985, 88(2):545-548
- Radha MH, Laxmipriya NP. Evaluation of biological properties and clinical effectiveness of Aloe vera: A systematic review. *J Tradit Complement Med.* 2014, 5(1):21-26
- Rauwald HW, Hoenig J, Flindt S, Geck P. Different influence of certain anthraquinones / anthrones on energy metabolism: an approach for interpretation of known synergistic effects in laxative action? *Planta Med* 1992, 58(1):A587-A588
- Remington JP, Wood HC *et al.*, editors. The Dispensatory of the United States of America. Aloe U.S. Br. 1918

- Reynolds T, Dweck AC. Aloe vera leaf gel: a review update. *J Ethnopharmacol.* 1999, 68(1-3):3-37
- Riecken EO, Zeitz M, Emde C, Hopert R, Witzel L, Hintze R, et al. The effect of an anthraquinone laxative on colonic nerve tissue: A controlled trial in constipated women. *Z Gastroenterol* 1990, 28:660-664
- Riemann JF, Schmidt H, Zimmermann W. The fine structure of colonic submucosal nerves in patients with chronic laxative abuse. *Scand J Gastroenterol* 1980, 15(6):761-768
- Riemann JF, Schmidt H. Ultrastructural changes in the gut autonomic nervous system following laxative abuse and in other conditions. *Scand J Gastroenterol* 1982, 71:111-124
- Roberts MC, Milikan RC, Galanko JA, Martin C, Sandler RS. Constipation, laxative use, and colon cancer in a North Carolina population. *Am J Gastroenterol* 2003, 98(4):857-864
- Schempp CM, Schoepf E, Simon JC. Durch Pflanzen ausgelöste toxische und allergische Dermatitis (Phyto dermatitis) [Plant-induced toxic and allergic dermatitis (phyto dermatitis)]. *Der Hautarzt* 2002, 53(2):93–97 [German]
- Schoerhuber M, Richter M, Dutter A, Sontag G, Marian B. Effect of anthraquinone-laxatives on the proliferation and urokinase secretion of normal, premalignant and malignant colonic epithelial cells. *European Journal of Cancer* 1998, 34(7):1091-1098
- Shah AH, Qureshi S, Tariq M, Ageel AM. Toxicity Studies on six plants used in the traditional Arab System of Medicine. *Phytother Res.* 1989 Vol 3 (1):25-29
- Shamim S, Ahmed SW, Azhar I. Antifungal activity of *Allium*, *Aloe*, and *Solanum* species. *Pharmaceutical Biology* 2004, 42(7):491-498
- Siegers CP, von Hertzberg-Lottin E, Otte M, Schneider B. Anthranoid laxative abuse – a risk for colorectal cancer? *Gut* 1993, 34(8):1099-1101
- Siegers CP, Siemers J, Baretton G. Sennosides and aloin do not promote dimethylhydrazine-induced colorectal tumours in mice. *Pharmacology* 1993, 47(1):205-208
- Smith B. Effect of irritant purgatives on the myentric plexus in man and mouse. *Gut* 1968, 9:139-145
- Sonnenberg A, Mueller AD. Constipation and cathartics as risk factors of colorectal cancer: A meta-analysis. *Pharmacology* 1993, 47(1):224-233
- Stolk LM, Hoogtanders K. Detection of laxative abuse by urine analysis with HPLC and diode array detection. *Pharm World Sci.* 1999, 21(1):40-43
- Tanaka H, Morooka N, Haraikawa K, Ueno Y. Metabolic activation of emodin in the reconstituted cytochrome P-450 system of the hepatic microsomes of rats. *Mutat Res.* 1987, 176(2):165-170
- Tavares IA, Mascolo N, Izzo AA, Capasso F. Effects of anthraquinone derivatives on PAF release by human gastrointestinal mucosa *in vitro*. *Phytotherapy Research* 1996, 10 (Suppl.1):S20-S21
- The British Pharmaceutical Codex, published by direction of the Council of the Pharmaceutical Society of Great Britain. Aloe 1911
- United States Pharmacopeia: Aloe, USP 38, NF 33, Vol 2, p 2096
- Vanderperren B, Rizzo M, Angenot L, Haufried V, Jadoul M, Hantson P. Acute liver failure with renal impairment related to the abuse of senna anthraquinone glycosides. *Ann Pharmacotherapy* 2005, 39(7-8):1353-1357

- Von Koenen E. Heil- und Giftpflanzen in Südwestafrika. Akademischer Verlag Windhoek S.W.A. 1977, 52
- Waldhäusl W, Kleinberger G, Korn A, Dudczak R, Bratusch-Marrain P, Nowotny P. Severe hyperglycemia: effects of rehydration on endocrine derangements and blood glucose concentration. *Diabetes* 1979, 28:577–584
- Wang HW, Chen TL, Yang PC, Ueng TH. Induction of cytochromes P450 1A1 and 1B1 by emodin in human lung adenocarcinoma cell line CL5. *Drug Metab Dispos.* 2001, 29(9):1229-1235
- Wassermann L, Avigad S, Beery E, Nordenberg J, Fenig E. The effect of aloe emodin on the proliferation of a new merkel carcinoma cell line. *The American Journal of Dermatopathology* 2002, 24(1):17-22
- Watt JM, Breyer-Brandwijk MG. The Medicinal and Poisonous Plants of South and East Africa, 2. Auflage, Livingstone, Edinburgh 1962, 921-923
- Westendorf J, Marquardt H, Poginsky B, Dominiak M, Schmidt J, Marquardt H. Genotoxicity of naturally occurring hydroxyanthraquinones. *Mutation Research* 1990, 240:1-12
- WHO monographs on selected medicinal plants. Vol. 1. Aloe. World Health Organization. Geneva 1999, 33-42
- Willems M, van Buuren HR, de Krijger R. Anthranoid self-medication causing rapid development of melanosis coli. *The Netherlands Journal of medicine* 2003, 61(1):22-24
- Williams CL, Dwyer J, Agostoni C, Hillemeier C, Kimm SYS, Kwiterovich PO, *et al.* A summary of conference recommendations on dietary fiber in childhood: Conference on Dietary Fiber in Childhood, New York (New York, USA), May 24, 1994. *Pediatrics* 1995, 96:1023-1028
- Wintola OA, Sunmonu TO, Afolayan AJ. The effect of Aloe ferox Mill. in the treatment of loperamide-induced constipation in Wistar rats. *BMC Gastroenterol.* 2010, 10:95
- Wintola OA, Sunmonu TO, Afolayan AJ. Toxicological evaluation of aqueous extract of Aloe ferox Mill. in loperamide-induced constipated rats. *Hum Exp Toxicol.* 2011, 30(5):425-431
- Woelfle D, Schmutte C, Westendorf J, Marquardt H. Hydroxyanthraquinones as tumour promoters: enhancement of malignant transformation of C3H mouse fibroblasts and growth stimulation of primary rat hepatocytes. *Cancer Research* 1990, 50(20):6540-6544
- Yagi A, Takeo S. Anti-inflammatory constituents, aloesin and aloemmannan in Aloe species and effects of tanshinon VI in Salvia miltiorrhiza on heart. *Journal of the Pharmaceutical Society of Japan* 2003, 123(7):517–532 [Japanese]
- Yagi T, Yamauchi K, Kuwano S. The synergistic purgative action of aloe-emodin anthrone and rhein anthrone in mice: synergism in large intestinal propulsion and water secretion. *J. Pharm. Pharmacol.* 1997, 49(1):22-25
- Yokohira M, Matsuda Y, Suzuki S, Hosokawa K, Yamakawa K, Hashimoto N, *et al.* Equivocal colonic carcinogenicity of Aloe arborescens Miller var. natalensis berger at high-dose level in a Wistar Hannover rat 2-y study. *J Food Sci.* 2009, 74:T24–T30

References evaluated, but not cited in the Assessment Report:

Anderson FA. Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of Aloe Andongensis Extract, Aloe Andongensis Leaf Juice, Aloe Arborescens Leaf Extract, Aloe Arborescens Leaf Juice, Aloe Arborescens Leaf Protoplasts, Aloe Barbadensis Flower Extract, Aloe Barbadensis Leaf, Aloe Barbadensis Leaf Extract, Aloe Barbadensis Leaf Juice, Aloe Barbadensis Leaf Polysaccharides, Aloe Barbadensis Leaf Water, Aloe Ferox Leaf Extract, Aloe Ferox Leaf Juice, and Aloe Ferox Leaf Juice Extract. *Int J Toxicol*. 2007, 26 (Suppl.2):1-50

Arroll B. Cochrane Corner Treatment for irritable bowel. *Nzfp* 2005, 32 (5):342

AWMF Leitlinie: Chronische Obstipation bei Erwachsenen Registernummer. Registernummer 021 – 019 S2k. Available at: <http://www.awmf.org/leitlinien/detail/II/021-019.html>. Accessed 16/04/15 [German]

AWMF Leitlinie: Reizdarmsyndrom: Definition, Pathophysiologie, Diagnostik und Therapie. Registernummer 021 – 016. Available at: <http://www.awmf.org/leitlinien/detail/II/021-016.html>. Accessed 16/04/15 [German]

Bharucha AE, Pemberton JH, Locke GR. American Gastroenterological Association technical review on constipation. *Gastroenterology* 2013, 144:218–238

Bharucha AE, Dorn SD, Lembo A, Pressman A. American Gastroenterological Association Medical Position Statement on Constipation. Available at: <http://www.gastrojournal.org/article/S0016-5085%2812%2901545-4/fulltext>. Accessed April 2015

Bharucha AE, Locke GR, Zinsmeister AR, Seide BM, McKeon K, Schleck CD, *et al*. Differences between painless and painful constipation among community women. *Am J Gastroenterol*. 2006, 101(3):604-612

Boudreau MD, Beland FA. An evaluation of the biological and toxicological properties of Aloe barbadensis (miller), Aloe vera. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*. 2006, 24(1):103-154

Breiner-Goldstein E, Evron Z, Frenkel M, Cohen K, Meiron KN, Peer D, *et al*. Targeting anthracycline-resistant tumor cells with synthetic aloe-emodin glycosides. *ACS Med Chem Lett*. 2011; 2(7):528-31

Brown JP. A review of the genetic effects of naturally occurring flavonoids, anthraquinones and related compounds. *Mutation Research* 1980, 75:243–277

Brunet C, Thomas P, Sielezneff I, Ugarte S, Giudicelli R, Sastre B, *et al*. [Subcutaneous cervical emphysema: complication of constipation. Review of the literature]. *J Chir (Paris)*. 1995; 132(4):198-200

Brusick D, Mengs U. Assessment of the genotoxic risk from laxative senna products. *Environ Mol Mutagen*. 1997, 29(1):1-9

Cameron BD, Phillips MW, Fenerty CA. Milk transfer of rhein in the rhesus monkey. *Pharmacology*. 1988; 36 Suppl.1:221-5

Camilleri M. Dyspepsia, irritable bowel syndrome, and constipation: review and what's new. *Rev Gastroenterol Disord*. 2001, 1(1):2-17

Camilleri M, Bharucha AE. Behavioural and new pharmacological treatments for constipation: getting the balance right. *Gut* 2010, 59(9):1288–1296

- Capasso F, Borelli F, Capasso R, Di Carlo G, Izzo AA, Pinto L, *et al.* Aloe and its Therapeutic Use. *Phytotherapy Research* 1998, 12:124-127
- Chen R, Zhang J, Hu Y, Wang S, Chen M, Wang Y. Potential antineoplastic effects of Aloe-emodin: a comprehensive review. *Am J Chin Med.* 2014, 42(2):275-288
- Cheng WC, Bian ZX, Zhu LX, Wu JCY, Sung JJ. Efficacy of Chinese herbal proprietary medicine (hemp seed pill) for functional constipation. *Am J Gastroenterol* 2011; 106: 120-1299
- Chicouri M and Chicouri I Demande de Brevet Nr de enregistrement nationale: 89 05688 de 28 avril 1989 Institut national de la propriété industrielle Paris
- Choi HC, Kim SJ, Son KY, Oh BJ, Cho BL. Metabolic effects of aloe vera gel complex in obese prediabetes and early non-treated diabetic patients: randomized controlled trial. *Nutrition* 2013; 29(9):1110-4
- Delmulle L, Demeyer K editors. Anthraquinones in plants: source, safety and applications in gastrointestinal health, 2nd ed. Nottingham University Press, Nottingham 2010, pdf e-book
- Dentali S. "Nondecolorized" essential qualifier for NTP aloe vera study material. *Toxicol Sci.* 2013, 133(2):342
- Dettmar PW, Sykes J. A multi-centre, general practice comparison of ispaghula husk with lactulose and other laxatives in the treatment of simple constipation. *Curr Med Res Opin.* 1998; 14(4):227-33
- Deutsche Gesellschaft für Neurogastroenterologie und Motilität, Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten. S2k-Leitlinie chronische Obstipation: Definition, Pathophysiologie, Diagnostik und Therapie. 021/019-S2k-Leitlinie Chronische Obstipation 2013, 1-55
- Di Palma JA, Cleveland MV, McGowan J, Herrera JL. A randomized, multicenter comparison of polyethylene glycol laxative and tegaserod in treatment of patients with chronic constipation. *Am J Gastroenterol.* 2007; 102(9):1964-71
- Frexinos J, Staumont G, Fioramonti J, Bueno L. Effects of sennosides on colonic myoelectrical activity in man. *Dig Dis Sci.* 1989; 34(2):214-9
- Finocchiaro C, Pezzana A, Galletti R, Costantino A, Malfi G, Demagistris A. [Role of diet in the treatment of constipation. Review of the literature]. *Minerva Dietol Gastroenterol.* 1989; 35(3):165-70
- Fintelmann V and Haase W. Chronisch habituelle Obstipation. *Ärztliche Praxis* 1977XXIX Jahrg. Nr 2 vom 4.1.1977 25-26
- Fioramonti J, Bueno L. Toxicity of laxatives: how to discriminate between myth and fact? *Eur J Gastroenterol Hepatol.* 1995; 7(1):5-7
- Fogleman RW, Chapdelaine JM, Carpenter RH, McAnalley BH. Toxicologic evaluation of injectable acemannan in the mouse, rat and dog. *Vet Hum Toxicol.* 1992a, 34(3):201-205
- Fogleman RW, Shellenberger TE, Balmer MF, Carpenter RH, McAnalley BH. Subchronic oral administration of acemannan in the rat and dog. *Vet Hum Toxicol.* 1992b, 34(2):144-147
- Furukawa F, Nishikawa A, Chihara T, Shimpo K, Beppu H, Kuzuya H, *et al.* Chemopreventive effects of Aloe arborescens on N-nitrosobis(2-oxopropyl)amine-induced pancreatic carcinogenesis in hamsters. *Cancer Lett.* 2002; 178(2):117-22
- Garg SK, Saksena SK, Chaudhury R. Antifertility screening of Plants Part VI: Effect of five indigenous plants on early pregnancy in Albino Rats. *Indian J Med Res* 58:1285-1289

- Gladman MA, Lunniss PJ, Scott SM, Swash M. Rectal hyposensitivity. *Am J Gastroenterol*. 2006; 101(5):1140-51
- Gorkom van BA, Karrenbeld A, van der Sluis T, Zwart N, de Vries EG, Kleibeuker JH. Apoptosis induction by sennoside laxatives in man; escape from a protective mechanism during chronic sennoside use? *J Pathol*. 2001; 194(4):493-9
- Harlev E, Nevo E, Lansky EP, Ofir R, Bishayee A. Anticancer potential of aloes: antioxidant, antiproliferative, and immunostimulatory attributes. *Planta Med*. 2012, 78(9):843-852
- Heidemann A, Miltenburger HG, Mengs U. The genotoxicity status of senna. *Pharmacology*. 1993, 47 (Suppl.1):178-186
- IARC Monograph. Aloe Vera. Available at: <http://monographs.iarc.fr/ENG/Monographs/vol108/mono108-01.pdf>. Accessed 15/01/16
- Lee KH, Kim JH, Lim DS, Kim CH. Anti-leukaemic and anti-mutagenic effects of di (2-ethylhexyl) phthalate isolated from Aloe vera Linne. *J Pharm Pharmacol* 2000, 52(2):593-598
- Leung FW. Etiologic factors of chronic constipation: review of the scientific evidence. *Dig Dis Sci*. 2007; 52(2):313-6
- Masuda T, Haraikawa K, Morooka N, Nakano S, Ueno Y. 2-Hydroxyemodin, an active metabolite of emodin in the hepatic microsomes of rats. *Mutation Research* 1985, 149(3):327-332
- Mengs U, Grimminger W, Krumbiegel G, Schuler D, Silber W, Völkner W. No clastogenic activity of a senna extract in the mouse micronucleus assay. *Mutat Res*. 1999, 444(2):421-426
- Müller-Lissner S. and Wald A. Constipation in Adults. *BMJ Clin Evid*.; 2010. pii: 0413.
- Paneitz A, Westendorf J. Anthranoid contents of rhubarb (*Rheum undulatum* L.) and other Rheum species and their toxicological relevance. *Eur Food Res Technol* 1999, 210:97–101
- Pasricha PJ. Drugs affecting gastrointestinal function. Stimulant (Irritant) Laxatives. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. Section VI (37). Eleventh edition. New York 2006, 994
- Petticrew M, Watt I, Sheldon T. Systematic review of the effectiveness of laxatives in the elderly. *Health Technol Assess*. 1997; 1(13):i-iv, 1-52
- Preston DM, Lennard-Jones JE. Anismus in chronic constipation. *Dig Dis Sci*. 1985; 30(5):413-8
- Preston DM, Lennard-Jones JE. Severe chronic constipation of young women: 'idiopathic slow transit constipation'. *Gut* 1986; 27(1):41-8
- Quarero AO, Meiniche-Schmidt V, Muris J, Rubin G, de Wit N. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. *The Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD003460.pub2.DOI: 10.1002/14651858.CD003460.pub2
- Rao SS, Welcher KD, Leistikow JS. Obstructive defecation: a failure of recto anal coordination. *Am J Gastroenterol*. 1998; 93(7):1042-50
- Ravi K, Bharucha AE, Camilleri M, Rhoten D, Bakken T, Zinsmeister AR. Phenotypic variation of colonic motor functions in chronic constipation. *Gastroenterology*. 2010; 138(1):89-97
- Richardson J, Smith JE, McIntyre M, Thomas R, Pilkington K. Aloe vera for preventing radiation-induced skin reactions: a systematic literature review. *Clin Oncol*. 2005; 17(6):478-84

Ruepert L, Quartero AO, de Wit NJ, van der Heijden GJ, Rubin G, Muris JW. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*. 2011 , (8):CD003460. doi: 10.1002/14651858.CD003460.pub3.

Sendelbach LE. A review of the toxicity and carcinogenicity of anthraquinone derivatives. *Toxicology* 1989, 57(3):227-240

Siegers CP. Anthranoid laxatives and colorectal cancer. *Trends Pharmacol Sci*. 1992; 13(6):229-31

Sitzmann FC, Buettner M, Dockter G. Lokale Nebenwirkungen an der Haut durch Anthraglykoside. *Pädiatr Prax* 1979, 21:355-358 [German]

Smith B. Pathologic changes in the colon produced by anthraquinone purgatives. *Dis Colon Rectum*. 1973; 16(6):455-8

Speare GS. Melanosis coli; experimental observations on its production and elimination in twenty-three cases. *Am J Surg*. 1951; 82(5):631-7

Spiller R, Aziz Q, Creed F, Emmanuel A, Houghton L, Hungin P, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. *Gut* 2007, 56:1770–1798

Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. *Aliment Pharmacol Ther*. 2011; 33(8):895-901

Syed T. A, Afzal M, Ashfaq Ahmad S, Holt AH, Ahmad SA, Ahmad SH. Management of genital herpes in men with 0.5% Aloe vera extract in a hydrophilic cream: A placebo-controlled double-blind study. *Journal of Dermatological Treatment* 1997, 8:99-102

Syed T. A., Ashfaq Ahmad S, Holt AH, Ahmad SA, Ahmad SH, Afzal M. Management of psoriasis with Aloe vera extract in a hydrophilic cream: a placebo-controlled, double-blind study, *Tropical Medicine & International Health* 1996, 4:9-505

Tarpila S, Tarpila A, Groehn P, Silvennoinen T, Lindberg L. Efficacy of ground flaxseed on constipation in patients with irritable bowel syndrome. *Current Topics in Nutraceutical Research* 2004, 2:119-125

Tomasin R, Gomes-Marcondes MC. Oral administration of Aloe vera and honey reduces Walker tumour growth by decreasing cell proliferation and increasing apoptosis in tumour tissue. *Phytother Res*. 2011, 25(4):619-623

Viera AJ, Wouk N. Potassium Disorders: Hypokalemia and Hyperkalemia. *Am Fam Physician*. 2015, 92(6):487-495

Vogler BK, Ernst E. Aloe vera: a systematic review of its clinical effectiveness. *Br J Gen Pract*. 1999, 49(447):823-828

Yan M, Zhang LY, Sun LX, Jiang ZZ, Xiao XH. Nephrotoxicity study of total rhubarb anthraquinones on Sprague Dawley rats using DNA microarrays. *J Ethnopharmacol*. 2006, 107(2):308-311

Yeh FT, Wu CH, Lee HZ. Signalling pathway for aloe-emodin-induced apoptosis in human H460 lung non-small carcinoma cell. *International Journal of Cancer* 2003, 106(1):26–33