

5 May 2015  
EMA/HMPC/36892/2014  
Committee on Herbal Medicinal Products (HMPC)

## List of references supporting the assessment of *Capsicum annuum* L. var. *minimum* (Miller) Heiser and small fruited varieties of *Capsicum frutescens* L., fructus

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.**

Aasvang EK, Hansen JB, Malmstrøm J, Asmussen T, Gennevois D, Struys MM, et al. The effect of wound instillation of a novel purified capsaicin formulation on postherniotomy pain: a double-blind, randomized, placebo-controlled study. *Anesth Analg* 2008, 107(1):282-291

Ahuja KDK, Ball MJ. Effects of daily ingestion of chilli on serum lipoprotein oxidation in adult men and women. *Br J Nutr* 2006, 96(2):239-242

Ahuja KD, Robertson IK, Geraghty DP, Ball MJ. The effect of 4-week chilli supplementation on metabolic and arterial function in humans. *Eur J Clin Nutr* 2007, 61(3):326-333

Akagi A, Sano H, Uehara H, Minami T, Otsuka H, Izumi K. Non-carcinogenicity of Capsaicinoids in B6C3F1 mice. *Food Chem Toxicol* 1998, 36(12):1065-1071

Altman RD, Aven A, Holmburg CE, Pfeifer LM, Sack M, Young GT. Capsaicin cream 0.025% as monotherapy for osteoarthritis: a double-blind study. *Sem Arthr Rheum* 1994, 6(Suppl. 3):25-33

Altomare DF, Rinaldi M, La Torre F, Scardigno D, Roveran A, Canuti S, et al. Red hot chili pepper and hemorrhoids: The explosion of a myth: Results of a prospective, randomized, placebo-controlled, crossover trial. *Dis Colon Rectum* 2006, 49(7):1018-1023

Al-Dahmesh B, Dkhil MA, Al-Quraishi S. Chili pepper-induced injury to splenic tissue of rabbit. *J Med Plants Res* 2011, 5 (10):2015-2020 (only abstract available)

Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanism of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth* 2011, 107(4):490-502

Archer VE, Jones DW. Capsaicin pepper, cancer and ethnicity. *Med Hypothes* 2002, 59(4):450-457

Atkinson ME, Chaggar JS. The effects of prenatal capsaicin on the distribution of substance P in developing primary afferent neurons. *Neurosci Lett* 1983, 36(1):26-29 (only abstract available)



- Babbar S, Marier JF, Mouksassi MS, Beliveau M, Vanhove GF, Chanda S, *et al.* Pharmacokinetic analysis of capsaicin after topical administration of a high-concentration capsaicin patch to patients with peripheral neuropathic pain. *Ther Drug Monit* 2009, 31(4):502-510
- Babbar S, Chanda S, Bley K. Inhibition and induction of human cytochrome P450 enzymes *in vitro* by capsaicin. *Xenobiotica* 2010, 40(12):807-816 (only abstract available)
- Backonja M, Wallace MS, Blonsky ER, Cutler BJ, Malan P Jr, Rauck R, *et al.* NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. *Lancet Neurol* 2008, 7(12):1106-1112
- Backonja MM, Malan TP, Vanhove GF, Tobias JK; C102/106 Study Group. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind, controlled study with an open-label extension. *Pain Med* 2010, 11(4):600-608
- Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Millikan LE. Topical capsaicin treatment of chronic postherpetic neuralgia. *J Am Acad Dermatol* 1989, 21(2 Pt 1):265-270
- Biesbroeck R, Bril V, Hollander P, Kabadi U, Schwartz S, Singh SP, *et al.* A double-blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy. *Adv Ther* 1995, 12(2):111-120
- Biro T, Acs G, Modarres S, Blumberg M. Recent advances in understanding of vanilloid receptors: a therapeutic target for treatment of pain and inflammation in skin. *J Investig Dermatol Symp Proc* 1997, 2:56-60
- Blaschek W, Ebel S, Hackenthal E, Holzgrabe U, Keller K, Reichling J, *et al.* HagerROM 2012: Hagers Handbuch der Drogen und Arzneistoffe. Springer-Verlag, Heidelberg 2012
- Bley K, Boorman G, Mohammad B, McKenzie D, Babbar S. A Comprehensive Review of the Carcinogenic and Anticarcinogenic Potential of Capsaicin. *Toxicol Pathol* 2012, 40:847-873
- Bölcskei K, Tékus V, Dézsi L, Szolcsányi J, Petho G. Antinociceptive desensitizing actions of TRPV1 receptor agonists capsaicin, resiniferatoxin and N-oleoyldopamine as measured by determination of the noxious heat and cold thresholds in the rat. *Eur J Pain* 2010, 14(5):480-486 (only abstract available)
- Bortolotti M, Coccia G, Grossi G, Miglioli M. The treatment of functional dyspepsia with red pepper. *Aliment Pharmacol Ther* 2002, 16(6):1075-1082
- Bortolotti M, Porta S. Effect of red pepper on symptoms of irritable bowel syndrome: Preliminary study. *Dig Dis Sci* 2011, 56(11):3288-3295
- Bouraoui A, Brazier JL, Zouaghi H, Rousseau M. Theophylline pharmacokinetics and metabolism in rabbits following single and repeated administration of Capsicum fruit. *Eur J Drug Metab Pharmacokin* 1995, 20(3):173-178 (only abstract available)
- Capsaicin Study Group. Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. *Arch Intern Med* 1991, 151(11):2225-2229
- Capsaicin Study Group. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. *Diabetes Care* 1992, 15(2):159-165
- Castle NA. Differential inhibition of potassium currents in rat ventricular myocytes by capsaicin. *Cardiovascular Res* 1992, 26(11):1137-1144
- Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaic receptor: a heat-activated ion channel in the pain pathway. *Nature* 1997, 389:816-824

Chanda S, Erexon G, Riach C, Innes D, Stevenson F, Murli H, et al. Genotoxicity studies with pure trans-capsaicin. *Mutat Res* 2004, 557:85-97

Chanda S, Sharper V, Hoberman A, Bley K. Developmental toxicity study of pure trans-capsaicin in rats and rabbits. *Int J Toxicol* 2006, 25:205-217

Chanda S, Erexon G, Frost D, Babbar S, Burlew JA, Bley K. 26-week dermal oncogenicity study evaluating pure trans-capsaicin in Tg.AC.hemizygous mice (FBV/N). *Int J Toxicol* 2007, 26:123-133 (only abstract available)

Chanda S, Bashir M, Babbar S, Koganti A, Bley K. *In vitro* hepatic and skin metabolism of capsaicin. *Drug Metab Dispos* 2008, 36(4):670-675

Cho JH, Brodsky M, Kim EJ, Cho YJ, Kim KW, Fang JY, et al. Efficacy of a 0.1% capsaicin hydrogel patch for myofascial neck pain: a double-blinded randomized trial. *Pain Med* 2012, 13(7):965-970

Chou CC, Wu YC, Wang YF, Chou MJ, Kuo SJ, Chen DR. Capsaicin-induced apoptosis in human breast cancer MCF-7 cells through caspase-independent pathway. *Oncol Rep* 2009, 21(3):665-671

Chrubasik S, Weiser T, Beime B. Effectiveness and safety of topical capsaicin cream in the treatment of chronic soft tissue pain. *Phytother Res*. 2010, 24(12):1877-1885

Chularojmontri L, Suwatronnakorn M, Wattanapitayakul SK. Influence of capsicum extract and capsaicin on endothelial health. *J Med Assoc Thailand = Chotmaihet thangphaet* 2010, 93(Suppl 2):S92-101 (only abstract available)

Cianchetti C. Capsaicin jelly against migraine pain. *Int J Clin Pract* 2010, 64(4):457-459

Colvin C, Wang CF, Soens MA, Mitani AA, Strichartz G, Gerner P. Prolonged cutaneous analgesia with transdermal application of amitriptyline and capsaicin. *Reg Anesth Pain Med* 2011, 36:236-240

Cruz L, Castaneda-Hernandez G, Navarrete A. Ingestion of chilli pepper (*Capsicum annuum*) reduces salicylate bioavailability after oral aspirin administration in the rat. *Can J Physiol Pharmacol* 1999, 77:441-446 (only abstract available)

De AK, Ghosh JJ. Acute capsaicin treatment causes alteration in rat lung lipids. *Med Sci Res* 1988, 16(17):929-930 (only abstract available)

Deal CL, Schnitzer TJ, Lipstein E, Seibold JR, Stevens RM, Levy MD, et al. Treatment of arthritis with topical capsaicin: a double-blind trial. *Clin Ther* 1991, 13(3):383-395

Debrezeni A, Abdel-Salam OME, Figler M, Juricskay I, Szolcsanyi J, Mozsik G. Capsaicin increases gastric emptying rate in healthy human subjects measured by <sup>13</sup>C-labeled octanoic acid breath test. *J Physiol (Paris)* 1999, 93:455-460

Del Bianco E, Geppetti P, Zippi P, Isolani D, Magini B, Cappugi P. The effects of repeated dermal application of capsaicin to the human skin on pain and vasodilatation induced by intradermal injection of acid and hypertonic solutions. *Br J Clin Pharmacol* 1996, 41(1):1-6

Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD010111. DOI: 10.1002/14651858.CD010111

Derry S, Rice AS C, Cole P, Tan T, Moore RA. Capsaicin applied to the skin for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD007393. DOI: 10.1002/14651858.CD007393.pub3

De Stefano R, Selvi E, Frati E, Cosentino R, Manganelli S, Manca S, et al. Efficacy of topical capsaicin in the treatment of Raynaud's phenomenon: A preliminary study. *Reumatismo* 1997, 49(2):107-111 (only abstract available)

Díaz Barriga Arceo S, Madrigal-Bujaidar E, Calderón Montellano EC, Ramírez Herrera L, Díaz García BD. Genotoxic effects produced by capsaicin in mouse during subchronic treatment. *Mutat Res* 1995, 345(3-4):105-109

Dini D, Bertelli G, Gozza A, Forno GG. Treatment of the post-mastectomy pain syndrome with topical capsaicin. *Pain* 1993, 54(2):223-226

Dkhil MA, Al-Quraishy S. Effects of extensive consumption of hot red pepper fruit on liver of rabbit. *J Med Plants Res* 2010, 4(23):2533-2538

Donnerer J, Amman R, Schuligoi R, Lembeck F. Absorption and metabolism of capsaicinoids following intragastric administration in rats. *Naunyn Schmiedeberg's Arch Pharmacol* 1990, 342:357-361 (only abstract available)

Dou D, Ahmad A, Yang H, Sarkar FH. Tumor cell growth inhibition is correlated with levels of capsaicin present in hot peppers. *Nutr Cancer* 2011, 63(2):272-281

Dwivedi V, Shrivastava R, Hussain S, Ganguly C, Bharadwaj M. Cytotoxic potential of Indian spices (extracts) against esophageal squamous carcinoma cells. *Asian Pacific J Cancer Prev* 2011, 12(8):2069-2073

Ellis CN, Berberian B, Sulica VI, Dodd WA, Jarratt MT, Katz HI, et al. A double-blind evaluation of topical capsaicin in pruritic psoriasis. *J Am Acad Dermatol* 1993, 29(3):438-442

Ellison N, Loprinzi CL, Kugler J, Hatfield AK, Miser A, Sloan JA, et al. Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. *J Clin Oncol* 1997, 15(8):2974-2980

Ericson A, Nur EM, Petersson F, Kechagias S. The effects of capsaicin on gastrin secretion in isolated human antral glands: Before and after ingestion of red chilli. *Digest Dis Sci* 2009, 54(3):491-498

European Pharmacopeia, 8<sup>th</sup> ed. Capsicum – Capsici fructus. Council of Europe. 01/2014: 1859

European Pharmacopeia, 8<sup>th</sup> ed. Capsicum oleoresin, refined and standardised – Capsici oleoresina raffinata et normata. Council of Europe. 01/2014: 2336

European Pharmacopeia, 8<sup>th</sup> ed. Capsicum soft extract, standardised – Capsici extractum spissum normatum. Council of Europe. 01/2014: 2529

European Pharmacopeia, 8<sup>th</sup> ed. Capsicum tincture, standardised – Capsici tinctura normata. Council of Europe. 01/2014: 2337

Fang JY, Wu PC, Huang YB, Tsai YH. *In vivo* percutaneous absorption of capsaicin, nonivamide and sodium nonivamide acetate from ointment bases: pharmacokinetic analysis in rabbits. *Int J Pharmaceut* 1996, 128:169-177

Forst T, Pohlmann T, Kunt T, Goitom K, Schulz G, Löbig M, et al. The influence of local capsaicin treatment on small nerve fibre function and neurovascular control in symptomatic diabetic neuropathy. *Acta Diabetol* 2002, 39(1):1-6

Frerick H, Keitel W, Kuhn U, Schmidt S, Bredehorst A, Kuhlmann M. Topical treatment of chronic low back pain with a capsicum plaster. *Pain* 2003, 106(1-2):59-64

Führer M, Vogelsang H, Hammer J. A placebo-controlled trial of an oral capsaicin load in patients with functional dyspepsia. *Neurogastroenterol Motil* 2011, 23(10):918-e397

Fusco BM, Alessandri M. Analgesic effect of capsaicin in idiopathic trigeminal neuralgia. *Anesth Analg* 1992, 74(3):375-377

Gagnier JJ. Evidence based review of natural health products for non-specific low back pain. *Open Pain J* 2010, 3(1):52-59

Gagnier JJ, Van Tulder MW, Berman B, Bombardier C. Herbal medicine for low back pain: A cochrane review. *Spine* 2007, 32(1):82-92

Gamse R. Capsaicin and nociception in the rat and mouse. Possible role of substance P. *Naunyn Schmiedebergs Arch Pharmacol* 1982, 320(3):205-216 (only abstract available)

Gerner P, Binshtok AM, Wang CF, Hevelone ND, Bean BP, Woolf CJ, et al. Capsaicin combined with local anesthetics preferentially prolongs sensory/nociceptive block in rat sciatic nerve. *Anesthesiol* 2008, 109:872-878

Gibbons CH, Wang N, Freeman R. Capsaicin induces degeneration of cutaneous autonomic nerve fibers. *Ann Neurol* 2010, 68:888-898

Glinsukon T, Stitmunnaithum V, Toskulkao C, Buranawuti T, Tangkrisanavinont V. Acute toxicity of capsaicin in several animal species. *Toxicon* 1980, 18:215-220

Gonlachanvit S, Fongkam P, Wittayalertpanya S, Kullavanijaya P. Red chili induces rectal hypersensitivity in healthy humans: Possible role of 5HT-3 receptors on capsaicin-sensitive visceral nociceptive pathways. *Aliment Pharmacol Ther* 2007, 26 (4):617-625

Gonlachanvit S, Mahayosnond A, Kullavanijaya P. Effects of chili on postprandial gastrointestinal symptoms in diarrhoea predominant irritable bowel syndrome: evidence for capsaicin-sensitive visceral nociception hypersensitivity. *Neurogastroenterol Motil* 2009, 21(1):23-32

Gooding SM, Canter PH, Coelho HF, Boddy K, Ernst E. Systematic review of topical capsaicin in the treatment of pruritus. *Int J Dermatol* 2010, 49(8):858-865

Graham DY, Anderson SY, Lang T. Garlic or jalapeno peppers for treatment of Helicobacter pylori infection. *Am J Gastroenterol* 1999, 94 (5):1200-1202

Gupta PJ. Consumption of red-hot chili pepper increases symptoms in patients with acute anal fissures. A prospective, randomized, placebo-controlled, double blind, crossover trial. *Arqu Gastroenterol* 2008, 45(2):124-127

Gupta PJ. Red hot chilli consumption is harmful in patients operated for anal fissure - A randomized, double-blind, controlled study. *Digest Surgery* 2007a, 24(5):354-357

Gupta PJ. Effect of red chili consumption on postoperative symptoms during the posthemorrhoidectomy period: Randomized, double-blind, controlled study. *World J Surgery* 2007b, 31(9):1822-1826

Han SS, Keum YS, Seo HJ, Chun KS, Lee SS, Surh YJ. Capsaicin suppresses phorbol ester-induced activation of NF-κB/Rel and AP-1 transcription factors in mouse epidermis. *Cancer Lett* 2001, 164(2):119-126

Hänsel R, Sticher O. *Pharmakognosie – Phytopharmazie*. 9th ed. Springer, Heidelberg, 2010

Harada N, Okajima K. Effect of topical application of capsaicin and its related compounds on dermal insulin-like growth factor -I levels in mice and on facial skin elasticity in humans. *Growth Hormone & IGF Res* 2007, 17:171-176

Hautkappe M, Roizen MF, Toledano A, Roth S, Jeffries JA, Ostermeier AM. Review of effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998, 14:97-106

Hayman M, Kam PCA. Capsaicin: a review of its pharmacology and clinical applications. *Curr Anaesth Crit Care* 2008, 19: 338-343

Hazardous Substances Data Bank: <http://toxnet.nlm.nih.gov>. Accessed 2015-02-03

Hiura A. Neuroanatomical effects of capsaicin on the primary afferent neurons. *Arch Histol Cytol* 2000, 63(3):199-215

Horowitz M, Wishart J, Maddox A, Russo A. The effect of chilli on gastrointestinal transit. *J Gastroenterol Hepatol* 1992, 7(1):52-56 (only abstract available)

Huynh HT, Teel RW. *In vitro* antimutagenicity of capsaicin toward heterocyclic amines in *Salmonella typhimurium* strain TA98. *Anticancer Res* 2005, 25(1A):117-120

Irving GA, Backonja MM, Duntzman E, Blonsky ER, Vanhove GF, Lu SP, et al. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. *Pain Med* 2011, 12(1):99-109

Irving G, Backonja M, Rauck R, Webster LR, Tobias JK, Vanhove GF. NGX-4010, a capsaicin 8% dermal patch, administered alone or in combination with systemic neuropathic pain medications, reduces pain in patients with postherpetic neuralgia. *Clin J Pain* 2012, 28(2):101-107

Islam MM, Zaman H, Rahaman D, Islam KMN. The effect of *Capsicum annuum* on gastric secretion in rats. *Bangladesh Med J* 1973, 1(3):79-86 (only abstract available)

Jang JJ, Devor DE, Logsdon DL, Ward JM. A 4-week feeding study of ground red chilli (*Capsicum annuum*) in male B6C3F1 mice. *Food Chem Toxicol* 1992, 30: 783-787 (only abstract available)

Jang HY, Kim SM, Yuk JE, Kwon OK, Oh SR, Lee HK, et al. *Capsicum annuum* L. methanolic extract inhibits ovalbumin-induced airway inflammation and oxidative stress in a mouse model of asthma. *J Med Food* 2011, 14(10):1144-1151

Jensen-Jarolim E, Gajdzik L, Haberl I, Kraft D, Scheiner O, Graf J. Hot spices influence permeability of human intestinal epithelial monolayers. *J Nutr* 1998, 128:577-581

Jordt SE, McKemy DD, Julius D. Lessons from peppers and peppermint: the molecular logic of thermosensation. *Current Opinion Neurobiology* 2003, 13:487-492

Kang JH, Tsuyoshi G, Le Ngoc H, Kim HM, Tu TH, Noh HJ, Kim CS, Choe SY, Kawada T, Yoo H, Yu R. Dietary capsaicin attenuates metabolic dysregulation in genetically obese diabetic mice. *J Med Food* 2011, 14(3):310-315

Kang JY, Alexander B, Math MV, Williamson RCN. The effect of chilli and its pungent ingredient capsaicin on gastrointestinal transit in the rat. *J Gastroenterol Hepatol* 1993, 8(6):513-516 (only abstract available)

Kang JY, Yeoh KG, Chia HP, Lee HP, Chia YW, Guan R. Chili - Protective factor against peptic ulcer? *Digest Dis Sci* 1995, 40(3):576-579 (only abstract available)

Keitel W, Frerick H, Kuhn U, Schmidt U, Kuhlmann M, Bredehorst A. Capsicum pain plaster in chronic non-specific low back pain. *Arzneimittelforschung/Drug Res* 2001, 51(11):896-903

Kennedy WR, Vanhove GF, Lu SP, Tobias J, Bley KR, Walk D, et al. A randomized, controlled, open-label study of the long-term effects of NGX-4010, a high-concentration capsaicin patch, on epidermal nerve fiber density and sensory function in healthy volunteers. *J Pain* 2010, 11(6):579-587

Kim KS, Koo MS, Jeon JW, Park HS, Seung IS. Capsicum plaster at the Korean hand acupuncture point reduces postoperative nausea and vomiting after abdominal hysterectomy. *Anesth Analg* 2002, 95(4):1103-1107

Kim CS, Park WH, Park JY, Kang JH, Kim MO, Kawada T, et al. Capsaicin, a spicy component of hot pepper, induces apoptosis by activation of the peroxisome proliferator-activated receptor γ in HT-29 human colon cancer cells. *J Med Food* 2004, 7(3):267-273

Kim KS, Kim DW, Yu YK. The effect of capsicum plaster in pain after inguinal hernia repair in children. *Paed Anaesth* 2006, 16(10):1036-1041

Kim KS, Nam YM. The analgesic effects of capsicum plaster at the Zusani point after abdominal hysterectomy. *Anesth Analg* 2006, 103(3):709-713

Kosuwon W, Sirichatiwapee W, Wisanuyotin T, Jeeravipoolvarn P, Laupattarakasem W. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. *J Med Assoc Thai* 2010, 93(10):1188-1195

Krogstad AL, Lönnroth P, Larson G, Wallin BG. Capsaicin treatment induces histamine release and perfusion changes in psoriatic skin. *Br J Dermatol* 1999, 141(1):87-93

Kyung MY, Jong OP, Kim GY, Yu R, In SH, Ju SA, et al. Capsaicin induces apoptosis by generating reactive oxygen species and disrupting mitochondrial transmembrane potential in human colon cancer cell lines. *Cell Mol Biol Lett* 2009, 14(3):497-510

Lawson T, Gannett P. The mutagenicity of capsaicin and dihydrcapsaicin in V79 cells. *Cancer Lett* 1989, 48(2):109-113

Lazzeri M, Beneforti P, Benaim G, Maggi CA, Lecci A, Turini D. Intravesical capsaicin for treatment of severe bladder pain: a randomized placebo controlled study. *J Urol* 1996, 156(3):947-952

Lee DC, Ryan JR. Magnesium-aluminum hydroxide suspension for the treatment of dermal capsaicin exposures. *Acad Emerg Med* 2003, 10(6):688-690

Lee YS, Kho HS, Kim YK, Chung SC. Influence of topical capsaicin on facial sensitivity in response to experimental pain. *J Oral Rehabil* 2007a, 34(1):9-14

Lee IO, Lee KH, Pyo JH, Kim JH, Choi YJ, Lee YC. Anti-inflammatory effect of capsaicin in Helicobacter pylori-infected gastric epithelial cells. *Helicobacter* 2007b, 12(5):510-517

Lee SH, Richardson RL, Dashwood RH, Baek SJ. Capsaicin represses transcriptional activity of β-catenin in human colorectal cancer cells. *J Nutr Biochem* 2012, 23(6):646-655

Liang YT, Tian XY, Chen JN, Peng C, Ma KY, Zuo Y, et al. Capsaicinoids lower plasma cholesterol and improve endothelial function in hamsters. *Eur J Nutr* 2013, 52(1):379-388

Lin CH, Lu WC, Wang CW, Chan YC, Chen MK. Capsaicin induces cell cycle arrest and apoptosis in human KB cancer cells. *BMC Complementary and Alternative Medicine* 2013, 13:46.

doi: 10.1186/1472-6882-13-46

Loeser J, Pilgram B, Dagtekin O. Chilli for therapy of trigeminus neuralgia. A case report (2012). *Schmerz* 2012, 26(4):435-437

Lotti T, Teofoli P, Tsampau D. Treatment of aquagenic pruritus with topical capsaicin cream. *J Am Acad Dermatol* 1994, 30(2 Pt 1):232-235

Low PA, Opfer-Gehrking TL, Dyck PJ, Litchy WJ, O'Brien PC. Double-blind, placebo-controlled study of the application of capsaicin cream in chronic distal painful polyneuropathy. *Pain* 1995, 62(2):163-168

Luqman S, Meena A, Marler LE, Kondratyuk TP, Pezzuto JM. Suppression of tumor necrosis factor- $\alpha$ -induced nuclear factor  $\kappa$ b activation and aromatase activity by capsaicin and its analog capsazepine. *J Med Food* 2011, 14(11):1344-1351

Lynn B, Ye W, Cotsell B. The actions of capsaicin applied topically to the skin of the rat on C-fibre afferents, antidromic vasodilatation and substance P levels. *Br J Pharmacol* 1992, 107(2):400-406 (only abstract available)

Lysy J, Sistiery-Ittah M, Israelit Y, Shmueli A, Strauss-Liviatan N, Mindrul V, et al. Topical capsaicin--a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. *Gut* 2003, 52(9):1323-1326

Magnusson BM, Koskinen LD. *In vitro* percutaneous penetration of topically applied capsaicin in relation to *in vivo* sensation responses. *Int J Pharm* 2000, 195(1-2):55-62

Makhloogh A, Ala S, Haj-Heydari Z, Kashi Z, Bari A. Topical capsaicin therapy for uremic pruritus in patients on hemodialysis. *Iran J Kidney Dis* 2010, 4(2):137-140

Malagarie-Cazenave S, Olea-Herrero N, Vara D, Morell C, Díaz-Laviada I. The vanilloid capsaicin induces IL-6 secretion in prostate PC-3 cancer cells. *Cytokine* 2011, 54(3):330-337

Marks DR, Rapoport A, Padla D, Weeks R, Rosum R, Sheftell F, et al. A double-blind placebo-controlled trial of intranasal capsaicin for cluster headache. *Cephalalgia* 1993, 13(2):114-116

Mason L. Systematic review of topical capsaicin in the treatment of chronic pain. *BMJ* 2004, 328:991-994

Mathew A, Gangadharan P, Varghese C, Nair MK. Diet and stomach cancer: A case-control study in South India. *Eur J Cancer Prev* 2000, 9(2):89-97

Mathias BJ. Topical capsaicin for chronic neck pain. *Am J Phys Med Rehab* 1995, 74:39-44

McCarthy GM, McCarty DJ. Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. *J Rheumatol* 1992, 19(4):604-607

McCleane G. The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study. *Eur J Pain* 2000a, 4(4):355-360

McCleane G. Topical application of doxepin hydrochloride, capsaicin and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. *Br J Clin Pharmacol* 2000b, 49:574-579

McCormack PL. Capsaicin dermal patch in non-diabetic peripheral neuropathic pain. *Drugs* 2010, 70:1831-1842

McMahon SB, Lewin G, Bloom SR. The consequences of long-term topical capsaicin application in the rat. *Pain* 1991, 44:301-310

- Meneghini CL, Angelini G. Contact allergy to antirheumatic drugs. *Contact Derm* 1979, 5(3):197-198
- Menéndez L, Lastra A, Hidalgo A, Baamonde A. The analgesic effect induced by capsaicin is enhanced in inflammatory states. *Life Sci* 2004, 74(26):3235-3244
- Milke P, Diaz A, Valdovinos MA, Moran S. Gastroesophageal reflux in healthy subjects induced by two different species of chilli (*Capsicum annuum*). *Dig Dis* 2006, 24(1-2):184-188
- Min JK, Han KY, Kim EC, Kim YM, Lee SW, Kim OH, et al. Capsaicin Inhibits *in Vitro* and *In Vivo* Angiogenesis. *Cancer Res* 2004, 64(2):644-651
- Misra MN, Pullani AJ, Mohamed ZU. Prevention of PONV by acustimulation with capsicum plaster is comparable to ondansetron after middle ear surgery. *Can J Anesth* 2005, 52(5):485-489
- Mizrak SC, Gadella BM, Erdost H, Ozer A, van Pelt AM, van Dissel-Emiliani FM. Spermatogonial stem cell sensitivity to capsaicin: An *in vitro* study. *Reprod Biol Endocrinol* 2008, 6:52
- Mohammadian P, Andersen OK, Arendt-Nielsen L. Correlation between local vascular and sensory changes following tissue inflammation induced by repetitive application of topical capsaicin. *Brain Res* 1998, 792(1):1-9
- Moller AT, Feldt-Rasmussen U, Rasmussen AK, Sommer C, Hasholt L, Bach FW, et al. Small-fibre neuropathy in female Fabry patients: reduced allodynia and skin blood flow after topical capsaicin. *J Peripher Nerv Syst* 2006, 11(2):119-125
- Morris GC, Gibson SJ, Helme RD. Capsaicin-induced flare and vasodilatation in patients with post-herpetic neuralgia. *Pain* 1995, 63(1):93-101
- Mózsik G, Szolcsányi J, Rácz I. Gastroprotection induced by capsaicin in healthy human subjects. *World J Gastroenterol* 2005, 11(33):5180-5184
- Muhiddin KA, Gallen IW, Harries S, Pearce VR. The use of capsaicin cream in a case of erythromelalgia. *Postgrad Med J* 1994, 70(829):841-843
- Myers BM, Smith JL, Graham DY. Effect of red pepper and black pepper on the stomach. *Am J Gastroenterol* 1987, 82(3):211-214 (only abstract available)
- Nakadaira H, Lang I, Szentirmay Z, Hitre E, Kaster M, Yamamoto M. A Case-Control Study of Gallbladder Cancer in Hungary. *Asian Pacific J Cancer Prev* 2009, 10 (5):833-836
- Nelson AJ, Ragan BG, Bell GW, Ichiyama RM, Iwamoto GA. Capsaicin-Based Analgesic Balm Decreases Pressor Responses Evoked by Muscle Afferents. *Med Sci Sports Exercise* 2004, 36(3):444-450
- Nevius E, Srivastava PK, Basu S. Oral ingestion of Capsaicin, the pungent component of chili pepper, enhances a discreet population of macrophages and confers protection from autoimmune diabetes. *Mucosal Immunol* 2012, 5(1):76-86
- N.N. Final report on the safety assessment of *Capsicum annuum* extract, *Capsicum annuum* fruit extract, *Capsicum annuum* resin, *Capsicum annuum* fruit powder, *Capsicum frutescens* fruit, *Capsicum frutescens* fruit extract, *Capsicum frutescens* resind, and capsaicin. *Int J Toxicol* 2007, 26(Suppl. 1):3-106
- Nolano M, Simone DA, Wendelschafer-Crabb G, Johnson T, Hazen E, Kennedy WR. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. *Pain* 1999, 81(1-2):135-145

Okumi H, Tashima K, Matsumoto K, Namiki T, Terasawa K, Horie S. Dietary agonists of TRPV1 inhibit gastric acid secretion in mice. *Planta Med* 2012, 78(17):1801-1806

Paice JA, Ferrans CE, Lashley FR, Shott S, Vizgirda V, Pittrak D. Topical capsaicin in the management of HIV-associated peripheral neuropathy. *J Pain Symptom Manage*, 2000, 19(1):45-52

Park KK, Chun KS, Yook JIN, Surh YJ. Lack of tumor promoting activity of capsaicin, a principal pungent ingredient of red pepper, in mouse skin carcinogenesis. *Anticancer Res* 1998, 18(6 A):4201-4205 (only abstract available)

Park HS, Kim KS, Min HK, Kim DW. Prevention of postoperative sore throat using capsicum plaster applied at the Korean hand acupuncture point. *Anaesthesia* 2004, 59 (7):647-651

Park KK, Surh YJ. Effects of capsaicin on chemically-induced two-stage mouse skin carcinogenesis. *Cancer Lett* 1997, 114:183-184

Patanè S, Marte F, Di Bella G, Cerrito M, Coglitore S. Capsaicin, arterial hypertensive crisis and acute myocardial infarction associated with high levels of thyroid stimulating hormone. *Int J Cardiol* 2009, 134(1):130-132

Patanè S, Marte F, La Rosa FC, La Rocca R. Capsaicin and arterial hypertensive crisis. *Int J Cardiol* 2010, 144(2):e26-e27

Peikert A, Henrich M, Ochs G. Topical 0.025% capsaicin in chronic post-herpetic neuralgia: efficacy, predictors of response and long-term course. *J Neurol* 1991, 238(8):452-456

Pellicer F, Picazo O, Gómez-Tagle B, De La O IR. Capsaicin or feeding with red peppers during gestation changes the thermonociceptive response of rat offspring. *Physiol Behavior* 1996, 60(2):435-438

Pellicer F, Picazo O, León-Olea M. Effect of red peppers (*Capsicum frutescens*) intake during gestation on thermonociceptive response of rat offspring. *Behav Brain Res* 2001, 119:179-183

Perfumi M, Sparapassi L. Rat offspring treated prenatally with capsaicin do not show some of the irreversible effects induced by neonatal treatment with neurotoxins. *Pharmacol Toxicol* 1999, 84:66-71

Pershing LK, Reilly CA, Corlett JL, Crouch DJ. Effects of vehicle on the uptake and elimination kinetics of capsaicinoids in human skin *in vivo*. *Toxicol Appl Pharmacol* 2004, 200(1):73-81

Prakash UNS, Srinivasan K. Gastrointestinal protective effect of dietary spices during ethanol-induced oxidant stress in experimental rats. *Appl Physiol Nutr Metab* 2010, 35(2):134-141 (only abstract available)

Proudlock R, Thompson C, Longstaff E. Examination of the potential genotoxicity of pure capsaicin in bacterial mutation, chromosome aberration, and rodent micronucleus tests. *Environ Mol Mutagen* 2004, 44:441-447

Raccagni AA, Bardazzi F, Baldari U, Righini MG. Erythema-multiforme-like contact dermatitis due to capsicum. *Contact Derm* 1995, 33:353-354

Reilly DM, Green MR. Eicosanoid and cytokine levels in acute skin irritation in response to tape stripping and capsaicin. *Acta Derm Venereol* 1999, 79(3):187-190

Roghani M, Baluchnejadmojarad T, Sohrabi Z, Sadeghi M. Anti-hyperglycemic and hypolipidemic effect of oral administration of *Capsicum frutescens* in male STZ-diabetic rats. *J Med Plants* 2004, 3(10):47-52+XVII (only abstract available)

- Saito A, Yamamoto M. Acute oral toxicity of capsaicin in mice and rats. *J Toxicol Sci* 1996, 21:195-200
- Santos MM, Vieira-Da-Motta O, Vieira IJ, Braz-Filho R, Gonçalves PS, Maria EJ, et al. Antibacterial activity of *Capsicum annuum* extract and synthetic capsaicinoid derivatives against *Streptococcus mutans*. *J Nat Med* 2012, 66(2):354-356
- Sasamura T, Kuraishi Y. Peripheral and central actions of capsaicin and VR1 receptors. *Jpn J Pharmacol* 1999, 80:275-280
- Sayin MR, Karabag T, Dogan SM, Akpinar I, Aydin M. A case of acute myocardial infarction due to the use of cayenne pepper pills. *Wiener Klin Wochenschrift* 2012, 124(7-8):285-287
- Scheffler NM, Sheitel PL, Lipton MN. Treatment of painful diabetic neuropathy with capsaicin 0.075%. *J Am Podiatr Med Assoc* 1991, 81(6):288-293
- Simone DA, Ochoa J. Early and late effects of prolonged topical capsaicin on cutaneous sensibility and neurogenic vasodilatation in humans. *Pain* 1991, 47(3):285-294
- Simpson DM, Brown S, Tobias J; NGX-4010 C107 Study Group. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology* 2008, 70(24):2305-2313
- Singh S, Farhan Asad S, Ahmad A, Khan NU, Hadi SM. Oxidative DNA damage by capsaicin and dihydrocapsaicin in the presence of Cu(II). *Cancer Lett* 2001, 169(2):139-146
- Sluka KA. Stimulation of deep somatic tissue with capsaicin produces long-lasting mechanical allodynia and heat hypoalgesia that depends on early activation of the cAMP pathway. *J Neurosci* 2002, 22(13):5687-5693
- Solanke TF. The effect of red pepper (*Capsicum frutescens*) on gastric acid secretion. *J Surg Res* 1973, 15(6):385-390 (only abstract available)
- Ständer S, Luger T, Metze D. Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol.* 2001, 44(3):471-478
- Stücker M, Reuther T, Hoffmann K, Aicher B, Altmeyer P. The effect of the base on the kinetics of action of the capsaicinoid nonivamide: evaluation with a hyperemic test. *Skin Pharmacol Appl Skin Physiol* 1999, 12(5):289-298
- Summary of product characteristics (SmPC) Elastoplast Heat Plaster 11 mg medicated plaster. Available at: [http://mri.medagencies.org/download/DE\\_H\\_0254\\_001\\_FinalPI\\_3of3.pdf](http://mri.medagencies.org/download/DE_H_0254_001_FinalPI_3of3.pdf)
- Summary of product characteristics (SmPC) Qutenza 179 mg cutaneous patch. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000909/WC500040453.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000909/WC500040453.pdf)
- Suresh D, Srinivasan K. Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats. *Ind J Med Res* 2010, 131(5):682-691
- Szabó IL, Czimber J, Szolcsányi J, Mózsik G. Molecular pharmacological approaches to effects of capsaicinoids and of classical antisecretory drugs on gastric basal acid secretion and on indomethacin-induced gastric mucosal damage in human healthy subjects (mini review). *Curr Pharm Des* 2013, 19(1):84-89
- Szeimies RM, Stolz W, Wlotzke U, Korting HC, Landthaler M. Successful treatment of hydroxyethyl starch-induced pruritus with topical capsaicin. *Br J Dermatol* 1994, 131:380-382

Szolcsányi J. Forty years in capsaicin research for sensory pharmacology and physiology. *Neuropeptides* 2004, 38(6):377-384

Tandan R, Lewis GA, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. Effect on sensory function. *Diabetes Care* 1992a, 15(1):15-18

Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. Controlled study with long-term follow-up. *Diabetes Care* 1992b, 15(1):8-14

Tarng DC, Cho YL, Liu HN, Huang TP. Hemodialysis-related pruritus: a double-blind, placebo-controlled, crossover study of capsaicin 0.025% cream. *Nephron* 1996, 72(4):617-622

Tsai YH, Huang YB, Fang JY, Wu PC. Percutaneous absorption of capsaicin and its derivatives. *Drug Dev Indust Pharm* 1994, 20:719-730

Tsuchiya Y, Terao M, Okano K, Nakamura K, Oyama M, Ikegami K, et al. Mutagenicity and mutagens of the red chili pepper as gallbladder cancer risk factor in Chilean women. *Asian Pacific J Cancer Prev* 2011, 12(2):471-476

Tütüncü S, Özfiliz N. Distribution of the vanilloid (capsaicin) receptor type 1 in the capsaicin treated rat ovaries on different sexual development periods. *Revue Méd Vét*, 2011, 162(10):460-467

Villasenor IM, De Ocampo EJ. Clastogenicity of red pepper (*Capsicum frutescens* L.) extracts. *Mutation Res - Environ Mut Rel Subjects Incl Methodol* 1994, 312(2):151-155

Walker RA, McCleane GJ. The addition of glyceryltrinitrate to capsaicin cream reduces the thermal allodynia associated with the application of capsaicin alone in humans. *Neurosci Lett* 2002, 323(1):78-80

Wall PD. The central consequences of the application of capsaicin to one peripheral nerve in adult rat. *Acta Physiol Hung* 1987, 69(3-4):275-286 (only abstract available)

Watson CP, Evans RJ. The postmastectomy pain syndrome and topical capsaicin: a randomized trial. *Pain* 1992, 51(3):375-379

Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. *Clin Ther* 1993, 15(3):510-526

Webster LR, Malan TP, Tuchman MM, Mollen MD, Tobias JK, Vanhove GF. A multicenter, randomized, double-blind, controlled dose finding study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. *J Pain* 2010a, 11(10):972-982

Webster LR, Tark M, Rauck R, Tobias JK, Vanhove GF. Effect of duration of postherpetic neuralgia on efficacy analyses in a multicenter, randomized, controlled study of NGX-4010, an 8% capsaicin patch evaluated for the treatment of postherpetic neuralgia. *BMC Neurol* 2010b, 10:92

Webster LR, Peppin JF, Murphy FT, Lu B, Tobias JK, Vanhove GF. Efficacy, safety, and tolerability of NGX-4010, capsaicin 8% patch, in an open-label study of patients with peripheral neuropathic pain. *Diabetes Res Clin Pract* 2011, 93(2):187-197

Weisshaar E, Ziethen B, Gollnick H. Lack of efficacy of topical capsaicin in serotonin-induced itch. *Skin Pharmacol Appl Skin Physiol* 2000, 13(1):1-8

Weisshaar E, Dunker N, Gollnick H. Topical capsaicin therapy in humans with hemodialysis-related pruritus. *Neurosci Lett* 2003, 345(3):192-194

Winocur E, Gavish A, Halachmi M, Eli I, Gazit E. Topical application of capsaicin for the treatment of localized pain in the temporomandibular joint area. *J Orofac Pain* 2000, 14(1):31-36 (only abstract available)

Yamaguchi M, Yahagi N, Kato H, Takano F, Ohta T. Capsicum extract and its constituents modulated the production of immunoglobulins in Peyer's patch cells *ex vivo*. *J Funct Foods* 2010, 2(4):255-262

Yang HJ, Jang DJ, Hwang JT. Anti-diabetic effects of Korean red pepper via AMPK and PPAR- $\gamma$  activation in C2C12 myotubes. *J Funct Foods* 2012, 4(2):552-558

Yeoh KG, Kang JY, Yap I, Guan R, Tan CC, Wee A, et al. Chili protects against aspirin-induced gastroduodenal mucosal injury in humans. *Digest Dis Sci* 1995, 40(3):580-583 (only abstract available)

Yoshimura M, Yonehara N. Influence of capsaicin cream in rats with peripheral neuropathy. *Pharmacol Res* 2001, 44:105-111

Yoshitani SI, Tanaka T, Kohno H, Takashima S. Chemoprevention of azoxymethane-induced rat colon carcinogenesis by dietary capsaicin and rotenone. *Int J Oncol* 2001, 19(5):929-939 (only abstract available)

Zhang J, Nagasaki M, Tanaka Y, Morikawa S. Capsaicin inhibits growth of adult T-cell leukemia cells. *Leukemia Res* 2003, 27(3):275-283

Zhang R, Humphreys I, Sahu RP, Shi Y, Srivastava SK. *In vitro* and *in vivo* induction of apoptosis by capsaicin in pancreatic cancer cells is mediated through ROS generation and mitochondrial death pathway. *Apoptosis* 2008, 13(12):1465-1478

Zik B, Özgüden Akkoc CG, Tütüncü S, İlhan T, Yilmaztepe AO, et al. Effects of low dose capsaicin (CAP) on ovarian follicle development in prepubertal rat. *Revue Méd Vét* 2010, 161(6):288-294