Review

Cancer Research

The Two Faces of Capsaicin

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Abstract

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is the principal pungent component in hot peppers, including red chili peppers, jalapeños, and habaneros. Consumed worldwide, capsaicin has a long and convoluted history of controversy about whether its consumption or topical application is entirely safe. Conflicting epidemiologic data and basic research study results suggest that capsaicin can act as a carcinogen or as a cancer preventive agent. Capsaicin is unique among naturally occurring irritant compounds because the initial neuronal excitation evoked is followed by a long-lasting refractory period, during which the previously excited neurons are no longer responsive to a broad range of stimuli. This process is referred to as desensitization and has been exploited for its therapeutic potential. Capsaicin-containing creams have been in clinical use for many years to relieve a variety of painful conditions. However, their effectiveness in pain relief is also highly debated and some adverse side effects have been reported. We have found that chronic, long-term topical application of capsaicin increased skin carcinogenesis in mice treated with a tumor promoter. These results might imply that caution should be exercised when using capsaicin-containing topical applications in the presence of a tumor promoter, such as, for example, sunlight. *Cancer Res; 71(8); 2809–14. ©2011 AACR.*

Introduction

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide; Fig. 1) is the principal pungent component in the fruits of plants from the genus *Capsicum,* which are members of the nightshade family, *Solanaceae*. These plants are native to the Americas and have been cultivated as part of its inhabitants' diet since at least 7500 BC (1). Capsaicin gives chili peppers their intensity or "hotness" when ingested or applied topically to the skin and is the primary ingredient in pepper spray, often used in law enforcement. The "heat" of chili peppers is measured in Scoville heat units (SHU), which are the number of times a chili extract must be diluted in water for it to lose its heat. Bell peppers rank lowest at 0 SHU, jalapeños score 3,000 to 6,000 SHU, and habaneros generate 300,000 SHU. Pure capsaicin, a hydrophobic, colorless, odorless, and crystalline-to-waxy solid at room temperature, measures 16,000,000 SHU. When consumed, capsaicin binds with pain receptors in the mouth and throat, which are normally responsible for sensing heat.

Capsaicin was first isolated in 1816 in partially purified crystalline form by Bucholz (2) and in pure crystalline form in 1876 by Thresh, who named it capsaicin (3). Buchheim (4) was the earliest to find that capsaicin caused a burning sensation when contacting mucous membranes and also increased secretion of gastric juice. The structure of capsaicin was partially solved by Nelson in 1919 (5), and the compound was originally synthesized in 1930 by Späth and Darling (6). Similar substances have since been isolated from chili peppers by Japanese chemists, who referred to them as capsaicinoids (7).

The chili is used extensively in Mexican and certain South American cuisines and was later adapted into Tex-Mex cuisine. Although unheard of in Africa and Asia until its introduction by Europeans, the chili pepper has since become an essential ingredient of numerous other cuisines, including those of Ethiopia, India, Indonesia, Korea, Laos, Malaysia, Pakistan, Southwest China, Sri Lanka, Thailand, and others.

Although widely consumed, capsaicin has a long and convoluted history of debate about whether its consumption or topical use is entirely safe. Conflicting epidemiologic and basic research studies suggest that capsaicin might play a role in either preventing cancer or causing cancer. Although some background information is provided about the controversial role of capsaicin, the primary focus of this review is not to discuss the extensive number of cellular, animal, and human studies done over the years, but rather to examine existing and new evidence suggesting that capsaicin might not be safe for long-term topical application in humans.

The Conflicting Role of Capsaicin Derived from Cell and Animal Studies

The majority of the literally hundreds of basic research studies suggest that capsaicin can induce cell-cycle arrest or apoptosis or inhibit proliferation in a variety of cancer cells, suggesting that it has potent chemopreventive activities (reviewed most recently in ref. 8). Despite all the work

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doi: 10.1158/0008-5472.CAN-10-3756

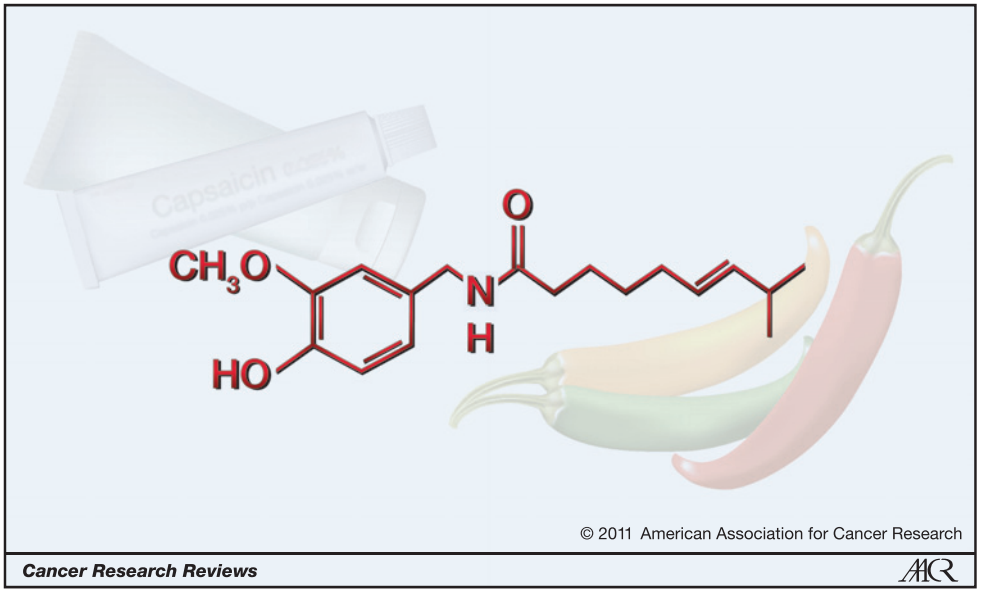

Figure 1. Capsaicin is the principal pungent component in hot peppers. Although it is widely consumed throughout the world, capsaicin has a long and convoluted history of controversy, showing two faces, about whether its consumption or topical application is entirely safe.

supporting a chemopreventive role for capsaicin in cancer cell culture models, a complete consensus about whether the primary effect of capsaicin is cancer prevention or causation has not yet been reached. However, capsaicin has also been reported to be mutagenic (9) and to induce an increase in the cell viability and proliferation of the androgen-responsive prostate cancer LNCaP cells corresponding with increased androgen receptor expression (10). This discrepancy might be due, at least partially, to the inherent difficulty, such as frequent need to renew primary cultures because of dedifferentiation, in studying the effects of capsaicin in relevant "normal cell" control groups for comparison with cancer cells, which are pathologic.

Animal studies have also yielded ambiguous results. Several studies have shown a carcinogenic effect. For example, approximately 60% of rats fed a semisynthetic diet, containing 10% chilies, developed neoplastic changes in the liver (11). Swiss albino mice fed capsaicin (0.03%) in a semisynthetic diet over their lifetime developed benign polypoid adenomas of the cecum (12). Capsaicin (0.002% in drinking water for 6 weeks) was reported to act as a promoter for the development of diethylnitrosamine-initiated, enzyme-altered foci in the liver of male rats (13). Chili extract has also been shown to have a promoting effect on the development of stomach and liver tumors in BALB/c mice initiated by methyl-acetoxy methylnitrosamine and benzene hexachloride, respectively (14). In another study, rats fed diets containing hot chili pepper showed slightly higher incidence of *N*-methyl-*N*-nitrosoguanidine–induced gastric cancer (15). Furthermore, systemic denervation of sensory neurons caused by treatment with capsaicin (125 mg/kg) resulted in significantly more lung and cardiac metastases in adult mice injected orthotopically with syngeneic 4T1 mammary carcinoma cells than was observed in vehicle-treated controls (16). In contrast, mice fed up to a 0.25% capsaicinoid mixture (64% capsaicin and 32.6% dihydrocapsaicin) in the diet for 79 weeks showed no evidence of carcinogenicity (17).

Capsaicin effectively inhibited tumor growth and induced apoptosis in nonobese diabetic severe combined immunodeficient mice (18) and, even when administered intraperitoneally (i.p.) to adult male mice over an 8-week period, had no mutagenic effects (19). Dermal application of capsaicin did not result in an increased incidence of preneoplastic or neoplastic skin lesions in male or female Tg.AC mice (20). Application of capsaicin followed by twice weekly applications of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) onto shaven backs of female ICR mice resulted in no significant increases in incidence and multiplicity of skin tumors. Repeated topical applications of capsaicin alone failed to promote 7,12dimethylbenz(a)anthracene (DMBA)–initiated mouse skin tumorigenesis but moderately inhibited the papilloma formation when given prior to each topical dose of phorbol ester (21). However, capsaicin was also reported to have no effect on preventing nitrosamine 4 (methylnitrosamino)I(3-pyridyl) 1 butanone (NNK)–induced lung tumor development (22). Overall, animal studies suggest no apparent relationship between mode of administration (i.e., i.p., oral, or topical application) and susceptibility to cancer development.

The Controversial Role of Capsaicin Obtained from Human Studies

In contrast to the results of cellular and animal studies, several epidemiologic studies seem to indicate that consumption of hot peppers, which contain various levels of capsaicin, might be associated with an increased risk of cancer, and especially gallbladder (23) or gastric cancer (24). However, the argument has been made that many of the epidemiologic studies had severe limitations, such as statistical imprecision of some analyses, potential misclassification of subjects by exposure, possible recall bias, or poor control of confounding

factors. Most are descriptive, correlative studies and draw speculative conclusions. Despite these limitations, the studies are cited continually in the literature as support for a cancer-promoting or causative effect of capsaicin. For example, red chili powder was found to be a risk factor for cancer of the oral cavity, pharynx, esophagus, and larynx in India (25). Significantly higher rates were observed for stomach and liver cancer in U.S. counties inhabited by Mexican-American, Cajun, white Creole, and black Creole ethnic–cultural groups who consume high levels of pepper compared with individuals who consume low amounts of hot peppers living in nearby and distant control counties matched for ethnic–cultural groups. From statistical analysis, the authors found a strong association between stomach cancer and capsaicin pepper (26). However, these authors also noted that other underlying unidentified ethnic, social, or cultural factors, for which high pepper use is a marker in the 3 different cultures, could be responsible for the observed associations. Researchers from Sungkyunkwan University (Seoul, Korea) proposed that capsaicin altered the metabolism of chemical carcinogens and might promote carcinogenesis at high doses (27). On the other hand, in an Italian case–control study, chili was briefly mentioned as being protective against stomach cancer (28). However, this finding was refuted by others (24), who indicated that chili peppers are not heavily consumed in northern Italy, where the study was conducted. In contrast, bladder biopsies from patients who were treated with capsaicin over a 5-year period were examined, and none of the bladder biopsies showed metaplasia, dysplasia, flat carcinoma *in situ*, papillary, or solid invasive cancer, suggesting a lack of carcinogenic activity by capsaicin (29).

Conflicting results about the effects of capsaicin on mucosal damage have also been observed. One study showed no mucosal erosions or other abnormalities after consumption of ground jalapeño peppers, even when placed directly in the stomach (30). In contrast, another study showed grossly visible gastric bleeding and mucosal microbleeding after consumption of red and black pepper (31).

Animal and cell models are potentially powerful preclinical tools in the study of the pharmacologic behavior of small molecules like capsaicin. The apparent disconnect between the animal, cellular, and human studies involving the effects of capsaicin emphasizes the recurrent difficulty in translating data obtained from cellular and animal studies to the human situation. For example, most cancer studies rely heavily on transformed cell lines or mouse models. Unfortunately, most cancer cell lines have adapted to long-term cell culture and undergone major changes in their genome. Most are likely aneuploid, which renders each cancer cell type unique in terms of gene and protein regulation and signaling and other biological behaviors. Even cell lines derived from the same tissue source can yield contradictory information, which makes the extrapolation of data from cell lines to the human patient meaningless. Transgenic and knockout mouse models are very powerful but also have substantial limitations. Overexpression or knockout of a particular gene can result in cellular adaptations that might be misleading. In addition, mouse and human tissues differ in many ways, including oncogene and oncoprotein signaling targets and susceptibility to malignant transformation. In addition, drugs and dietary factors are likely metabolized differently. Thus, the extrapolation of preclinical data to clinical reality remains challenging and capsaicin is no exception.

The Paradox of Topical Application of Capsaicin

Capsaicin is unique among naturally occurring irritant compounds because the initial neuronal excitation evoked is followed by a long-lasting refractory period, during which time the previously excited neurons are no longer responsive to a broad range of apparently unrelated stimuli (32). This process is referred to as desensitization and has been exploited for its therapeutic potential. In effect, capsaicin-containing creams have been in clinical use for many years to relieve painful conditions such as diabetic neuropathy (33). Capsaicin is the key ingredient in the experimental drug Adlea (ALRGX-4975; Anesiva, Inc.), which is in phase III trials as a long-acting analgesic to treat postsurgical and osteoarthritis pain for weeks to months after a single injection to the site of pain (34). Degeneration of epidermal nerve fibers has been suggested to contribute to the analgesic effect credited to capsaicin (35). A high-concentration (640 $\mu g/cm^2$) capsaicin patch [(NG-4010) Qutenza; NeurogesX, Inc.] has been clinically evaluated for managing peripheral neuropathic pain. Systemic capsaicin exposure after single 60- or 90-minute application was determined from plasma samples, and results revealed a relatively low systemic exposure and a short half-life ($\sim$1.6 hours) for capsaicin (36).

Topical capsaicin has been suggested as an effective pain management adjunct for rheumatoid arthritis, osteoarthritis, neuralgias, diabetic neuropathy, and other conditions including neural dysfunction, inflammation, and painful or itching cutaneous disorders resulting from surgery, injury, or tumors (33). However, even in this arena, evidence for the effectiveness or safety of capsaicin use in pain relief is controversial. Application of capsaicin to the skin causes an enhanced sensitivity to noxious stimuli, followed by a period with reduced sensitivity and, after repeated applications, persistent desensitization (37). Capsaicin-induced dermal pain is common after exposure to capsaicin-containing hot peppers, personal protection sprays, or topical creams (38). A condition known as "Hunan hand," which is a form of contact dermatitis, has been noted in workers handling peppers (39). When applied to glabrous lips or tongue, capsaicin elicits burning pain, the intensity of which corresponds with the degree of increased blood flow and temperature induced by capsaicin (40). On the one hand, capsaicin has also been shown to be an effective topical treatment for hemodialysis-induced pruritus (i.e., itching) in patients with end-stage renal disease (41). On the other hand, topical application of capsaicin was not effective in serotonin-induced itching in healthy volunteers (42).

Topical application of capsaicin has been used in cancer patients in the management of long-term neuropathic pain resulting from surgery (43). Patients received 8 weeks of a 0.075% capsaicin cream (4 times per day) followed by 8 weeks of an identical-looking placebo cream or vice versa. Most

patients preferred the capsaicin treatment over the placebo in spite of some toxic side effects that included coughing and burning and redness of the skin (43). Oral capsaicin in a candy (taffy) vehicle produced substantial temporary pain reduction in 11 patients with oral mucositis pain from cancer therapy (44). However, capsaicin was not effective in relieving pain accompanying HIV-associated distal symmetrical peripheral neuropathy (45).

In a review of double-blind placebo-controlled trials pooled for analysis of neuropathic conditions or musculoskeletal conditions, topically applied capsaicin exhibited moderate-to-poor efficacy (46). Notably, local administration of capsaicin resulted in adverse events or even in an increase of pain above tolerable levels in about one third of patients suffering from musculocutaneous or neuropathic pain (46). In addition, at least one coronary vasospasm and acute myocardial infarction, reportedly induced by the use of a topical capsaicin patch to relieve lower back pain, has been documented (47).

Cocarcinogenic Effect of Capsaicin

We recently reported that capsaicin has a cocarcinogenic effect on TPA-promoted skin carcinogenesis *in vivo* and is mediated not only through the transient receptor potential vanilloid subfamily member 1 (TRPV1), but also through the tyrosine kinase epidermal growth factor receptor (EGFR). Even though blockade of the TRPV1 has been suggested as a therapeutic approach to pain relief, TRPV1 is a widely expressed protein with a function that might be critical in various nonneuronal physiologic conditions. The EGFR is a receptor tyrosine kinase that is overexpressed in many human epithelial cancers and is a potential target for anticancer drugs. We showed that TRPV1 interacts with the EGFR, leading to EGFR degradation. The TRPV1 is the first membrane receptor shown to have a tumor-suppressing effect associated with the downregulation of another membrane receptor. Notably, the absence of TRPV1 in mice resulted in a striking increase in skin carcinogenesis. The data suggest that, although a great deal of interest has focused on TRPV1 as a target for pain relief, the chronic blockade of this pain receptor might increase the risk for skin cancer development (48).

Furthermore, we showed that topical application of capsaicin on the dorsal skin of DMBA-initiated and TPA-promoted TRPV1 wild-type (WT) and TRPV1 knockout (KO) mice not only induced skin tumors in WT mice, but also more and larger skin tumors in TRPV1/KO mice, suggesting an additional TRPV1-independent mechanism. Cyclooxygenase-2 (COX-2) was highly elevated by capsaicin treatment in tumors and murine embryonic fibroblasts from TRPV1/KO mice. Inhibitors of EGFR/MAP/ERK kinase signaling suppressed TPA/capsaicin–induced COX-2 expression in TRPV1/KO cells, indicating that activation of EGFR and its downstream signaling is involved in COX-2 elevation. Capsaicin induced a further induction of TPA-increased COX-2 expression in EGFR/WT cells, but not in EGFR/KO cells. TPA/capsaicin cotreatment caused EGFR tyrosine phosphorylation and activated EGFR downstream signaling, including extracellular signal regulated kinases (ERK) and Akt in EGFR/WT, but not EGFR/KO cells. Specific inhibition of EGFR and TRPV1 indicated that capsaicin-induced ERK activation in A431 cells was dependent on EGFR, but not TRPV1. Overall, these observations indicate that capsaicin not only acts through the TRPV1 as a cocarcinogen in TPA-induced skin carcinogenesis, but also exerts these effects by activating the EGFR and COX-2 (49).

The toxicity and safety of capsaicin and related compounds have been evaluated, and results have been presented in at least one international report (50). A major, but predictable, conclusion was that capsaicin is a skin irritant even at low concentrations. Skin irritation and other tumor-promoting effects of capsaicin seem to be mediated mainly through interaction with the TRPV1, and the authors suggested that a potent tumor promoter might also be a moderate-to-severe skin irritant. Thus, a limitation on capsaicin content in topical applications that would significantly reduce its skin irritation potential might be expected to lessen concerns relating to tumor promotion potential (50). Our results seem to support this recommendation. We conclude that capsaicin alone is not a carcinogen because topical application of capsaicin to the dorsal skin of mice in the absence of a tumor promoter produced no skin cancers. However, the data also suggest that total blockade of the TRPV1 for pain relief or chronic, long-term topical application of capsaicin might increase the risk of skin cancer, especially in the presence of a tumor promoter, such as, for example, sunlight.

Summary and Conclusions

The continuing controversy surrounding consumption or topical application of capsaicin clearly suggests that more well-controlled epidemiologic studies are needed to evaluate the safety and efficacy of capsaicin use. At the same time, one should note that hot pepper consumption is not equivalent to the use of pure capsaicin. Possible questions to be addressed might include determining the amount of capsaicin that is effective for specific pain types. Is capsaicin effective for all types of pain or only certain types of pain, or does the mode of administration determine its effectiveness? In future epidemiologic studies, the amount of capsaicin consumed or administered topically or by other means needs to be carefully monitored and, if possible, controlled. In addition to case–control studies, well-designed cohort prospective studies might be another alternative for acquiring useful information.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This work was supported by The Hormel Foundation and NIH grants CA077646, CA111536, CA120388, R37CA081064, and ES016548.

Received October 14, 2010; revised December 29, 2010; accepted January 14, 2011; published online April 12, 2011.

References

1. Perry L, Dickau R, Zarrillo S, Holst I, Pearsall DM, Piperno DR, et al. Starch fossils and the domestication and dispersal of chili peppers (Capsicum spp. L.) in the Americas. Science 2007;315:986–8.
2. Pereira J. Capsicum annuum. In: Carson J, editor. The elements of materia medica and therapeutics. 3rd ed. Philadelphia: Blanchard and Lea; 1854. p. 505–7.
3. Thresh JC. Isolation of capsaicin. The Pharmaceutical Journal and Transactions 1876;6:941–7.
4. Buchheim R. Fructus Capsici. Proceedings of the American Pharmaceutical Association. 1873;22:106.
5. Nelson EK. The constitution of capsaicin, the pungent principle of capsicum. J Am Chem Soc 1919;41:1115–21.
6. Späth S, Darling SF. Synthese des capsaicins. Chem Ber 1930;63B:737–43.
7. Kosuge S, Inagaki Y, Okumura H. Studies on the pungent principles of red pepper. Part VIII. On the chemical constitutions of the pungent principles. Nippon Nogeikagaku Kaishi 1961;35:923–7 [J Agric Chem Soc].
8. Oyagbemi AA, Saba AB, Azeez OI. Capsaicin: a novel chemopreventive molecule and its underlying molecular mechanisms of action. Indian J Cancer 2010;47:53–8.
9. Nagabhushan M, Bhide SV. Mutagenicity of chili extract and capsaicin in short-term tests. Environ Mutagen 1985;7:881–8.
10. Malagarie-Cazenave S, Olea-Herrero N, Vara D, Díaz-Laviada I. Capsaicin, a component of red peppers, induces expression of androgen receptor via PI3K and MAPK pathways in prostate LNCaP cells. FEBS Lett 2009;583:141–7.
11. Hoch-Ligeti C. Production of liver tumours by dietary means; effect of feeding chilies [Capsicum frutescens and annuum (Linn.)] to rats. Acta Unio Int Contra Cancrum 1951;7:606–11.
12. Toth B, Gannett P. Carcinogenicity of lifelong administration of capsaicin of hot pepper in mice. In Vivo 1992;6:59–63.
13. Jang JJ, Cho KJ, Lee YS, Bae JH. Different modifying responses of capsaicin in a wide-spectrum initiation model of F344 rat. J Korean Med Sci 1991;6:31–6.
14. Agrawal RC, Wiessler M, Hecker E, Bhide SV. Tumour-promoting effect of chilli extract in BALB/c mice. Int J Cancer 1986;38:689–95.
15. Kim JP, Park JG, Lee MD, Han MD, Park ST, Lee BH, et al. Cocarcinogenic effects of several Korean foods on gastric cancer induced by N-methyl-N'-nitro-N-nitrosoguanidine in rats. Jpn J Surg 1985;15:427–37.
16. Erin N, Boyer PJ, Bonneau RH, Clawson GA, Welch DR. Capsaicin-mediated denervation of sensory neurons promotes mammary tumor metastasis to lung and heart. Anticancer Res 2004;24[2B]:1003–9.
17. Akagi A, Sano N, Uehara H, Minami T, Otsuka H, Izumi K. Non-carcinogenicity of capsaicinoids in B6C3F1 mice. Food Chem Toxicol 1998;36:1065–71.
18. Ito K, Nakazato T, Yamato K, Miyakawa Y, Yamada T, Hozumi N, et al. Induction of apoptosis in leukemic cells by homovanillic acid derivative, capsaicin, through oxidative stress: implication of phosphorylation of p53 at Ser-15 residue by reactive oxygen species. Cancer Res 2004;64:1071–8.
19. Muralidhara NK, Narasimhamurthy K. Non-mutagenicity of capsaicin in albino mice. Food Chem Toxicol 1988;26:955–8.
20. Chanda S, Erexson 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;26:123–33.
21. Park KK, Surh YJ. Effects of capsaicin on chemically-induced two-stage mouse skin carcinogenesis. Cancer Lett 1997;114:183–4.
22. Teel RW, Huynh HT. Lack of the inhibitory effect of intragastrically administered capsaicin on NNK-induced lung tumor formation in the A.J mouse. In Vivo 1999;13:231–4.
23. Serra I, Yamamoto M, Calvo A, Cavada G, Báez S, Endoh K, et al. Association of chili pepper consumption, low socioeconomic status and longstanding gallstones with gallbladder cancer in a Chilean population. Int J Cancer 2002;102:407–11.
24. López-Carrillo L, Hernández Avila M, Dubrow R. Chili pepper consumption and gastric cancer in Mexico: a case-control study. Am J Epidemiol 1994;139:263–71.
25. Notani PN, Jayant K. Role of diet in upper aerodigestive tract cancers. Nutr Cancer 1987;10:103–13.
26. Archer VE, Jones DW. Capsaicin pepper, cancer and ethnicity. Med Hypotheses 2002;59:450–7.
27. Lee BM, Park KK. Beneficial and adverse effects of chemopreventive agents. Mutat Res 2003;523–524:265–78.
28. Buiatti E, Palli D, Decarli A, Amadori D, Avellini C, Bianchi S, et al. A case-control study of gastric cancer and diet in Italy. Int J Cancer 1989;44:611–6.
29. Dasgupta P, Chandiramani V, Parkinson MC, Beckett A, Fowler CJ. Treating the human bladder with capsaicin: is it safe? Eur Urol 1998;33:28–31.
30. Graham DY, Smith JL, Opekun AR. Spicy food and the stomach. Evaluation by videoendoscopy. JAMA 1988;260:3473–5.
31. Myers BM, Smith JL, Graham DY. Effect of red pepper and black pepper on the stomach. Am J Gastroenterol 1987;82:211–4.
32. Szallasi A, Cortright DN, Blum CA, Eid SR. The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. Nat Rev Drug Discov 2007;6:357–72.
33. Hautkappe M, Roizen MF, Toledano A, Roth S, Jeffries JA, Ostermeier AM. Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. Clin J Pain 1998;14:97–106.
34. Remadevi R, Szallisi A. Adlea (ALGRX-4975), an injectable capsaicin (TRPV1 receptor agonist) formulation for longlasting pain relief. IDrugs 2008;11:120–32.
35. 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;81:135–45.
36. 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;31:502–10.
37. Derry S, Lloyd R, Moore RA, McQuay HJ. Topical capsaicin for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2009;4:CD007393.
38. Kim-Katz SY, Anderson IB, Kearney TE, MacDougall C, Hudmon KS, Blanc PD. Topical antacid therapy for capsaicin-induced dermal pain: a poison center telephone-directed study. Am J Emerg Med 2010;28:596–602.
39. Williams SR, Clark RF, Dunford JV. Contact dermatitis associated with capsaicin: Hunan hand syndrome. Ann Emerg Med 1995;25:713–5.
40. Boudreau SA, Wang K, Svensson P, Sessle BJ, Arendt-Nielsen L. Vascular and psychophysical effects of topical capsaicin application to orofacial tissues. J Orofac Pain 2009;23:253–64.
41. Makhlough A. Topical capsaicin therapy for uremic pruritus in patients on hemodialysis. Iran J Kidney Dis 2010;4:137–40.
42. Weisshaar E, Ziethen B, Gollnick H. Lack of efficacy of topical capsaicin in serotonin-induced itch. Skin Pharmacol Appl Skin Physiol 2000;13:1–8.
43. 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;15:2974–80.
44. Berger A, Henderson M, Nadoolman W, Duffy V, Cooper D, Saberski L, et al. Oral capsaicin provides temporary relief for oral mucositis pain secondary to chemotherapy/radiation therapy. J Pain Symptom Manage 1995;10:243–8.
45. Paice JA, Ferrans CE, Lashley FR, Shott S, Vizgirda V, Pitrak D. Topical capsaicin in the management of HIV-associated peripheral neuropathy. J Pain Symptom Manage 2000;19:45–52.
46. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ 2004;328:991.
47. Akçay AB, Ozcan T, Seyis S, Acele A. Coronary vasospasm and acute myocardial infarction induced by a topical capsaicin patch. Turk Kardiyol Dern Ars 2009;37:497–500.

48. Bode AM, Cho YY, Zheng D, Zhu F, Ericson ME, Ma WY, et al. Transient receptor potential type vanilloid 1 suppresses skin carcinogenesis. Cancer Res 2009;69:905–13.
49. Hwang MK, Bode AM, Byun S, Song NR, Lee HJ, Lee KW, et al. Cocarcinogenic effect of capsaicin involves activation of EGFR signaling but not TRPV1. Cancer Res 2010;70:6859–69.
50. 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 resin, and capsaicin. Int J Toxicol 2007;26(Suppl 1):3–106.