



Red Pepper

Overview of Potential Health Benefits

Keith Singletary, PhD

Red peppers are part of a group of 20 plant species belonging to the genus *Capsicum* of the botanical family Solanaceae. The recognition that capsaicin can activate the transient receptor potential ion channel of the vanilloid type (TRPV1) has led to the use of red pepper extracts, capsaicin, and its analogs in pharmacological strategies for treating various medical conditions, especially pain and other neurological conditions. Interest in red pepper and capsaicin for dietary strategies to improve health has increased. The capacity of dietary capsaicin to manage gastrointestinal distress is unclear, because of a lack of understanding of its apparent contradictory actions within various segments of the gastrointestinal tract. More promising is evidence linking capsaicin and red pepper to improving weight loss and weight maintenance as well as lessening glucose intolerance and insulin resistance. However, progress in substantiating these benefits is limited by the need for larger, well-controlled human studies that can characterize capsaicin/red pepper's actions at doses more consistent with typical human intakes. Likewise, insights into both TRPV1-associated and TRPV1-independent mechanisms related to any health benefits of dietary red pepper have only begun to be explored. *Nutr Today*. 2011;46(1):33-47

Red peppers are part of a group of 20 plant species belonging to the genus *Capsicum* of the botanical family Solanaceae. Principal species used in foods are *Capsicum annuum* L and *Capsicum frutescens* L. Other species include *Capsicum chinense* Jacq, *Capsicum baccatum* L, and *Capsicum pubescens* Ruiz & Pav. Red pepper is native to South America and has been used by Native

Americans for medicinal and culinary purposes for thousands of years. *Capsicum* fruits could be considered one of the earliest uses of a food additive.^{1,2} There are records of Christopher Columbus, upon his return to Europe, naming a fruit he brought back from the New World “red pepper.” Its uses in traditional medicines have included treatments for sore throat, cough, toothache, stomach ailments, rheumatism, wound healing, and parasitic infections. Furthermore, the dried, ripe fruit of the *Capsicum* species provides ingredients for skin-conditioning agents, external analgesics, flavoring agents, cosmetic fragrances, and repellent sprays.²⁻⁸ There is a cultivar of red pepper, CH-19 sweet, which lacks the strong pungency or irritant properties of red pepper, yet appears to maintain similar biological activities.⁹

Red pepper actually encompasses a variety of plants with diverse common names that include chili pepper, tabasco pepper, African chilies, paprika, and cayenne pepper. *Capsicum* species can be eaten raw or dried, but commonly are consumed in ground, powdered form or in food supplemented with *Capsicum* oleoresin as an additive.¹⁰ The consumption of *Capsicum* fruit varies widely. For example, populations in Asia and Mexico have estimated daily intakes of the fruit between 5 and 15g. This is equivalent to intakes of the active ingredient capsaicin and related compounds (capsaicinoids) of approximately 2.5 to 150 mg/d. Capsaicin is the ingredient of red pepper that imparts the “hot” sensation to the tongue. Per capita European and US *Capsicum* consumption is estimated to be 0.05 to 0.5 g/d, or about 0.005 to 1.5 mg capsaicinoids per day.² Red pepper powder marketed in the United States may contain 3 to 4 mg capsaicinoids per gram. The capsaicin content of red pepper can vary considerably, depending on its pungency.⁴ For example, mild varieties of red pepper may contain 0.14% capsaicinoids (ie, 7 mg capsaicin per 5-g dried fruit) or less, whereas hot varieties may contain amounts of capsaicinoids in dried fruits as high as 0.6% to 1.0%. Information about the impact of food preparation and processing is limited. It is known that

drying temperatures greater than 70°C to 80°C can decrease red pepper pungency.²

The *Capsicum* fruit contains a number of pungent capsaicinoid compounds and biologically active constituents that are composed of the vanilloid derivative capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) and its analogs, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin.^{6,11} Capsaicin was isolated from *Capsicum* in 1846, and its structure was determined in 1919.¹² Capsaicin and dihydrocapsaicin constitute the predominant portion (90%) of these capsaicinoids. In plants, capsaicin purportedly plays a role in preventing microbial infections and suppressing unsuitable infestations¹³ as well as being a deterrent to predators.¹⁴ In Ch-19 sweet pepper, the 3 main analogs of capsaicin are capsiate, dihydrocapsiate, and nordihydrocapsiate. Whereas capsaicin's chemical structure consists of a vanillyl moiety conjugated to a fatty acid chain via an amide bond, in capsiate the 2 moieties are conjugated via an ester linkage.⁹ This seemingly small difference in structure largely accounts for the dramatic decrease in the pungency of CH-19 compared with other varieties of red pepper.

We now know how capsaicin makes red pepper taste hot, in part due to the discovery of the "capsaicin receptor" or the transient receptor potential ion channel of the vanilloid type (TRPV1) that is activated by capsaicin. This receptor was cloned in 1997 and was subsequently found to act as a molecular integrator of painful, noxious (nociceptive) stimuli often precipitating or accompanying inflammation. It is known that TRPV1 also responds to low pH (<5.5) and has a principal function as a noxious heat sensor.¹⁵ TRPV1 is embedded in primary afferent sensory nerve fibers and controls, as its name implies, the entry of Ca⁺⁺ and other ions, which can lead to changes in nerve concentrations of neuropeptides, such as substance P and calcitonin gene-related peptide. These neuromodulators are partially responsible for the sensitization and desensitization phenomena associated with TRPV1 activities.^{15,16} TRPV1 is expressed in some protein receptors, called nociceptors, which are present on sensory nerve terminals in the skin and which respond to noxious stimuli (intense mechanical, thermal, or chemical stresses) or other stimuli that are capable of damaging normal tissues.¹⁷ When activated, these sensory nerves carry pain signals and similar information to the spinal cord and brain. A paradoxical action of capsaicin is that it can both activate and inactivate (or desensitize) sensory neurons containing TRPV1. For example, with the skin, an initial topical application of capsaicin causes an activation-associated burning pain or itching sensation accompanied by cutaneous vasodilation due to stimulation of sensitive

sensory neurons. Repeated applications lead to reduced sensitivity and a refractory state or desensitization-linked analgesia. Based on numerous test systems, it is clear that in small doses capsaicin stimulates, whereas at high doses it impairs, capsaicin-sensitive afferent nerves.^{15,18,19} Desensitization may lead to excessive Ca⁺⁺ influx and consequent death of TRPV1-containing nociceptive neurons. This limits the usefulness of capsaicin and other TRPV1 agonists for management of pain in this context.^{4,7,20,21} In several areas of the brain, TRPV1-containing neurons have been identified. Their functions may include pain processing and central thermoregulation, although all roles are unknown. It is interesting that the nonpungent capsate analogs of capsaicin can activate TRPV1 and can induce nociceptive responses when injected subcutaneously in mice. Yet capsates do not induce irritant properties when applied to skin surfaces, the eyes, or oral cavity. The high lipophilicity of capsates and their instability in aqueous environments may contribute to their lack of pungency.²²

Also known as the vanilloid receptor, TRPV1 is expressed in other organs and nonneuronal tissues, such as bladder, kidney, spleen, heart, stomach, and even mast cells. The tissue distribution of this receptor suggests that it and its ligands may be involved in a wider variety of physiological functions than originally assumed, not only in sensing environmental stimuli, but also in functions related to cell proliferation and immune response.^{15,16,23} In fact, TRP ion channels, in general, are believed to have evolved as important sensory components of cells that can respond to numerous stimuli, including temperature, touch, sound, osmolarity, pheromones, taste, and pain.²⁴ Furthermore, TRPV1 expression is an important component in various disease states and conditions, such as inflammatory bowel disease, fecal urgency and urinary incontinence, gastrointestinal reflux disease, pancreatitis, interstitial cystitis, airway diseases, and chronic pain.^{17,25} Whether these changes in receptor expression contribute to or are a consequence of these conditions is not yet completely clear.

Many of capsaicin's effects are mediated by binding to TRPV1. Yet, capsaicin also has actions not related to its activity as a TRPV1 ligand. Red pepper and capsaicin can also affect the oxidant status of cells, can modulate the cell cycle, and can alter the activities of proinflammatory intermediates and intracellular signaling networks.²⁶⁻³³

Overview of Potential Health Benefits

Interest in red pepper and capsaicin for dietary strategies to improve health has recently increased, particularly in relation to energy balance and body weight maintenance. Table provides an overview of some of the potential

Table. Summary of Scientific Research

Scientific Evidence for Selected Uses	Rating
<p>Pain relief (pharmacological use)</p> <p>Capsaicin as an agonist of TRPV1 has been studied extensively as a pharmacological agent for pain relief. Capsaicin applied either as a cream or a patch is more effective in treating some pain conditions than others. For example, topical application of capsaicin is effective in managing postherpetic neuralgia. On the other hand, topical capsaicin may be only poorly or moderately effective in managing neuropathic pain induced by other conditions, and only may be useful for localized pain or as a third-line method of pain management. Numerous reviews have summarized the conditions under which capsaicin-containing pharmaceutical agents can best be used.^{20,25,34–46} Recently, capsaicin has been considered as an adjuvant in the treatment of postoperative pain.^{18,47–51} In general, enthusiasm for the topical use of capsaicin in clinical practice has been diminished because of the need to cotreat with a local anesthetic (to minimize initial burning, stinging sensations, and erythema), because of other transient adverse effects, such as sneezing and coughing, and because of the need for repeated daily applications.²⁰ These disadvantages of capsaicin have led to development of TRPV1 antagonists for managing pain that are without these adverse effects.^{15,17}</p>	Strong, convincing
<p>Effects on digestive tract</p> <p>Interest in possible effects of <i>Capsicum</i> components on the gastrointestinal (GI) tract in part stems from the realization that TRPV1 is expressed in numerous neurons innervating the GI tissues. Capsaicin-sensitive neurons are involved in the control of a variety of processes regulating GI homeostasis, such as circulation, secretion, motility, and sensing noxious stimuli (events capable of causing tissue damage), which provide an important mechanism for communications between the GI tract and the brain. Although the presence of TRPV1 may contribute to several pathologies of the GI tract (such as irritable bowel disease), TRPV1 may also have beneficial functions in mediating some anti-inflammatory responses to noxious agents.^{52,53} In this regard, capsaicin has been used as a pharmacological agent to probe the role of TRPV1 in normal gut physiology and disease.^{19,53,54}</p> <p>The responses of the GI tract to capsaicin are complex, dose dependent, and sometimes contradictory. An example of capsaicin's apparently contradictory effects is its role in dyspepsia and peptic ulcers. Red pepper and capsaicin are claimed to cause stomach irritation and damage. Yet, there is preclinical and clinical evidence that capsaicin may have beneficial actions in protecting against lesion formation in the gastric and intestinal mucosa in part by alleviating oxidative stress.^{53,55–61} Furthermore, capsiates derived from sweet pepper were found to inhibit nuclear factor κB activation and potently suppress inflammation in vivo in the glandular epithelium in the bowel of dextran sulfate-treated mice.⁶² Although application of capsaicin to the human small intestine can elicit pain, chronic oral administration of 2.5 g red pepper powder per day (1.75 mg capsaicin per day) to human volunteers decreased abdominal pain and symptoms of dyspepsia.^{53,57,63} The characterization of these opposing actions of capsaicin on the GI mucosa needs to be more fully elucidated, especially as affected by capsaicin dose, other dietary factors, length of capsaicin treatment and individual variability in sensitivity.^{53,64}</p>	Preliminary, inconclusive
<p>Obesity and diabetes</p> <p><i>Human energy balance studies</i></p> <p>Body weight loss and maintenance of a healthy body mass index (BMI) can contribute to reducing the prevalence of obesity. There is only limited epidemiological evidence associating consumption of capsaicin with lower prevalence of obesity.⁶⁵ The potential for spicy foods to enhance energy expenditure and thus alter energy balance was recognized as early as the 1980s, when it was reported that a meal containing 3 g of chili sauce and 3 g mustard sauce acutely increased metabolic rate by 25%, compared with</p>	Emerging, suggestive

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Table. Summary of Scientific Research, continued

Scientific Evidence for Selected Uses

Rating

those individuals consuming a nonspiced control meal.⁶⁶ The maximum increase in metabolic rate occurred after 75–90 min. Subsequent human studies focusing specifically on red pepper and capsaicin provided additional support for a beneficial action of capsaicin-containing spices on energy balance. For example, addition of 10 g red pepper (30 mg capsaicin) to a meal increased energy expenditure in human subjects for a short period (<4 h) after the meal.^{67,68} It is not clear from the literature whether people habituate to this effect of capsaicin-containing spice intake. The thermogenic effect in humans has been studied in few long-term studies, in part because, at least in white populations, compliance is problematic.⁶⁹ Similar results on energy balance were found when capsaicin was evaluated in combination with other biologically active ingredients, such as caffeine, calcium, and catechins, although this obscured the individual contribution of capsaicin.^{67,68} The impact of red pepper specifically on oxidation of carbohydrate, fat, and protein varied among studies.^{67,70–72} Nonpungent capsinoid compounds also have been reported to affect energy metabolism, sympathetic nervous activity, and fat oxidation, although the responses are inconsistent.^{73–77} Some of the variability in human responses to intake of *Capsicum* constituents may be due not only to dose effects but also to differences in BMI of subjects and the presence of genetic variants among populations.⁷⁵ Although substrate oxidation may be increased following capsaicin administration, weight loss or weight maintenance may not necessarily be significantly improved. For example, Lejeune et al⁷⁸ observed that when capsaicin was given at 135 mg/d for 3 mo following a 4-week weight-loss diet, weight gain was not significantly different than placebo controls, although fat oxidation was higher in the capsaicin group vs the placebo group.

Capsaicin’s effect on energy balance and substrate oxidation may be due to increased sympathetic nervous system activity, although the findings in this regard are inconsistent.⁶⁹ Furthermore, it is unclear how much of this effect of capsaicin on energy balance and weight changes is mediated by an agonist action on TRPV1.

Satiety may be another mediator of capsaicin’s effect on energy balance. For example, administration of 0.9 g red pepper before each of 3 meals (2.25 mg capsaicin per meal) to humans significantly increased satiety and suppressed 16-h energy intake approximately 10%.⁷⁹ The researchers observed a stronger reduction when capsaicin was provided orally in tomato juice as compared with ingestion of capsaicin-containing capsules, which suggests a sensory effect of capsaicin. However, in another study, the impact of capsaicin on decreased energy (fat) intake was determined to be independent of its spicy sensation in the mouth.⁸⁰ Similar satiety enhancement effects and reduction in energy intake were observed by others when an intake of 6–10 g red pepper per meal was examined.⁸¹ This 6- to 10-g red pepper intake would be considered high for US and European populations (usually <1-g/d intake). In contrast, levels of 8–15 g/d have been reported for Asian and Mexican populations. Similar to pungent red pepper cultivars, a nonpungent variation of red pepper (CH-19 sweet pepper) and a combination of green tea and capsaicin demonstrated energy-intake-reducing effects.⁸² In contrast, a lunch containing capsaicin (1.03-g red pepper equivalent to 80 000 Scoville heat units) did not acutely impact satiety⁸³ or energy expenditure. Interestingly, despite this lack of effect of the capsaicin-containing lunch on energy balance, blood levels of the gut-derived hormone GLP-1 increased, levels of ghrelin decreased, and no effect on circulating levels of peptide YY was observed. Characterization of the effects of capsaicin on these hormones is warranted for a better mechanistic insight into capsaicin’s potential actions on satiety.

Table. Summary of Scientific Research, continued

Scientific Evidence for Selected Uses	Rating
<i>Preclinical energy balance studies</i>	
<p>There is evidence from preclinical studies that capsaicin and <i>Capsicum frutescens</i> also influence energy homeostasis, adipogenesis, and obesity through a variety of mechanisms including activation of the TRPV1 receptor. Capsaicin administration in animal models affects energy intake, volume intake, and satiety control systems in a complex manner.^{84–90} Neonatal pharmacological administration of capsaicin to rodents is known to selectively destroy and desensitize TRPV1-containing sensory neurons.⁶³ Such animals have altered energy and thermal homeostasis.^{91,92} Capsinoids administered intragastrically (10 mg/kg body weight) to mice increased energy expenditure and thermogenesis, in part by activating small intestine extrinsic (spinal and vagus) nerves.⁹³ Early research in rats demonstrated that capsaicin desensitization of nerves led to a long-term decrease in accumulation of body fat and brown adipose tissue. This loss of function of capsaicin-sensitive nerves in treated animals resulted in an alteration in energy balance conducive to leanness. This was suggested to be due to a suppression of the age-associated increase in circulating calcitonin gene-related peptide (CGRP) from these nerves that can enhance obesity.^{94,95} This pharmacological evidence for the role of the capsaicin receptor in body fatness was supported by the observation that TRPV1-null mice are protected from diet-induced obesity.⁹⁶ There are additional experimental data that capsaicin administration can alter adiposity, blood flow, and regulation of adipocyte function.^{15,97,98} For example, dietary administration of capsaicin (0.01%) for 120 d prevented obesity in male wild-type mice but not in TRPV1 knockout mice fed a high-fat diet. This diet also affected TRPV1 regulation during adipogenesis.⁹⁹ Of interest, capsaicin may also be able to alter these obesity-associated processes independently of TRPV1.¹⁰⁰ Similar to findings for capsaicinoids, oral administration of capsiate to rats resulted in decreased abdominal fat content and enhanced muscle oxidative capacity. Uncoupling protein regulation in capsiate-treated animals was altered, but the changes were inconsistent.^{101–103} Oral capsiate administration to mice (10–50 mg/kg body weight) promoted energy metabolism, suppressed fat accumulation, and increased endurance swimming activity, in part by stimulating vanilloid receptors.^{104–106} Capsinoid and capsaicin administration reduced serum lipid levels in hyperlipidemic rats.¹⁰⁷</p>	
<i>Human diabetes studies</i>	
<p>Besides energy balance, capsaicin also has been reported to affect glucose and insulin homeostasis. For example, in a small study of 10 women, consumption of 5-g fresh <i>C frutescens</i>, an amount of red pepper not typically consumed in US and European diets, significantly inhibited the elevation of plasma glucose levels at 30 minutes after an oral dose of glucose, compared with drinking glucose alone.¹⁰⁸ In contrast, the opposite response of human plasma glucose levels to capsaicin intake was observed in another study.¹⁰⁹ In a study of 36 individuals consuming meals containing 30 g chili pepper (approximately 33 mg capsaicin per day), a reduced amount of insulin was needed to control a postprandial increase in glucose, an effect that was more apparent in subjects with BMI ≥ 26.3 kg/m² and when chili was consumed regularly.¹¹⁰ In a recent crossover study of 12 healthy volunteers in which the oral glucose tolerance test (OGTT) was performed, supplementation with 5 g <i>C frutescens</i> resulted in a significant lowering of plasma glucose concentrations and elevation of plasma insulin levels, compared with controls.¹¹¹</p>	
<i>Preclinical diabetes studies</i>	
<p>There is good preclinical evidence that TRPV1 is involved in serum glucose regulation, and, because TRPV1 is detected in the pancreas and beta islet cells, TRPV1 may be important in insulin release and diabetes.^{52,97} Early studies in rats and mice demonstrated that pharmacological treatment with high doses of capsaicin or similar drugs that inhibit neural TRPV1 activity retarded aging-induced insulin resistance and counteracted</p>	
	(continues)

Table. Summary of Scientific Research, continued

Scientific Evidence for Selected Uses	Rating
<p>diabetes-associated glucose intolerance.^{94,112} Subsequent reports describing capsaicin-induced desensitization of TRPV1-containing sensory nerves on glucose intolerance and insulin resistance in animal models are inconsistent. Dogs intravenously administered 9 mg capsaicin exhibited decreased blood glucose levels and elevated plasma insulin levels following the OGTT.¹¹³ Similar effects of capsaicin administration in mice (100 mg/kg body weight, subcutaneously) on blood glucose levels were observed, although no effect on plasma insulin concentration was noted after OGTT.¹¹⁴ Two studies in which capsaicin was fed to rodents (0.5–2.0 g <i>C frutescens</i>/100-g diet or 0.015% dietary capsaicin) resulted in mixed effects on blood glucose levels after a glucose tolerance test.^{115,116} Furthermore, capsaicin treatment resulted in inconsistent responses in circulating insulin concentrations. Diabetic rats fed a combination of red pepper and fermented soybeans showed improved glucose homeostasis that was associated with decreased insulin resistance, decreased hepatic fat storage, and activation of liver adenosine monophosphate kinase.¹¹⁷ Capsaicin's actions have been associated with a variety of mechanisms. It has been proposed that capsaicin may modulate enzymes regulating glucose metabolism or may affect hormone, neuropeptide, and cytokine levels. It also may impact insulin binding to its receptor.^{97,113,114,116–121} Differences in response to capsaicin or <i>Capsicum</i> spp may be a result of differing dosing protocols, dietary regimens, and animal models used among studies.</p>	
<p>Effects on cancer</p>	<p>Preliminary, inconclusive</p>
<p>The impact of red pepper and capsaicin on cancer is inconsistent. The epidemiological literature suggests that a high consumption of chili pepper is associated with increased risk for stomach cancer,^{122–124} liver cancer, bladder cancer, and pancreatic cancer, although results are not always consistent.^{6,125–130} In contrast, a case report suggested that capsaicin may slow prostate-specific antigen doubling time.¹³¹ Capsaicin and dihydrocapsaicin are mutagenic in an in vitro assay,^{33,132} and capsaicin can induce oxidative DNA damage.¹²⁵ Extracts of capsaicin have been reported to be cytotoxic and genotoxic.⁶ In contrast, a dietary mixture of capsaicinoids was found to be noncarcinogenic in a long-term mouse study.¹³³ The cancer-suppressive effects of red pepper on tumorigenesis have been observed in animal models, although individual effects on colon, stomach, and lung cancer are inconsistent.^{6,134–141} In general, effects of <i>Capsicum</i> and capsaicin on carcinogenesis in vivo are dose-dependent, and little is known preclinically about cancer outcomes at doses consumed in the typical human diet. Although animal studies on capsaicin and cancer are inconclusive, there is evidence mostly from in vitro studies that capsaicin and other capsaicinoids and capsates, alone or in combination with other bioactive compounds, can cause cell death in a variety of cancer cell lines.^{142–156} Moreover, capsaicin and analogs have received attention as potential cancer chemopreventive or chemotherapeutic agents.^{33,157–162} Oral capsaicin in a candy vehicle also has been reported to provide temporary relief for oral mucositis secondary to chemotherapy and radiation therapy.¹⁶³</p>	
<p>Miscellaneous effects (primarily pharmacological uses)</p>	<p>Preliminary, inconclusive</p>
<p>A subset of TRPV1-containing sensory neurons contain CGRP and substance P, which are demonstrated vasodilators and natriuretic/diuretic agents. Although a report detected a hypotensive effect of capsaicin when administered to SHR rats, there is little additional information to substantiate any benefit of this vanilloid in treating hypertension.¹⁶⁴ Capsaicin has the capacity to suppress cholera toxin production in <i>Vibrio cholerae</i> cells.¹⁶⁵ Capsaicin also can protect mouse neuromuscular junctions from the neuromuscular effects of <i>Clostridium botulinum</i> neurotoxin A.¹⁶⁶ On the other hand, jalapeno peppers were unable to successfully hamper <i>Helicobacter pylori</i> infection¹⁶⁷ or mitigate the adverse effects of HIV infection.¹⁶⁸</p>	

Table. Summary of Scientific Research, continued

Scientific Evidence for Selected Uses	Rating
<p>The clinical and preclinical efficacy of topical capsaicin in the pharmacological treatment of osteoarthritis is inconsistent.^{169–174} There is limited evidence for the use of capsaicin in the management of fibromyalgia.¹⁷⁵ Capsaicin has been considered for use in pharmacological strategies to manage urinary tract dysfunctions.^{53,176–178} Topical applications of capsaicin also was reported to effectively treat hemodialysis-induced pruritus in patients with end-stage renal disease.¹⁷⁹</p> <p>In mice, capsaicin administration stimulated sensory neurons in the brain and improved cognitive function, effects associated with increased insulinlike growth factor 1 (IGF-1) and CGRP levels, as well as enhanced angiogenesis and neurogenesis.¹⁸⁰ Capsaicin also demonstrated a neuroprotective effect in improving brain and liver dysfunction in a mouse model of hepatic failure.¹⁸¹ Intranasal application of capsaicin has been demonstrated to lessen migraine attacks in chronic migraine patients.¹⁸²</p> <p>Although known to be a tussive agent, capsaicin also has been studied for treatment of tonsillitis and rhinitis.^{52,183–187} <i>Capsicum</i> has been reported to prevent postoperative sore throat¹⁸⁸ and postoperative nausea and vomiting.^{189,190} Capsiates may be useful in triggering a swallowing reflex in elderly patients with aspiration pneumonia.¹⁹¹</p> <p>Topical application of capsaicin and related compounds may stimulate IGF-1 production in hair follicles of skin, potentially promoting hair growth, and may be useful in the treatment of skin disorders of patients with growth hormone deficiency and in the elderly.^{192,193}</p>	

health benefits of capsaicin. The recognition that capsaicin can activate TRPV1 has led to the use of capsaicin and its analogs in pharmacological strategies for treating various conditions, especially pain and other neurological conditions. Although some of these uses are strictly pharmacological, they nonetheless will be examined along with those having potential dietary benefits on health. Examples of various uses for capsaicin and red pepper are presented, and an effort is made to give an overview of the variety of scientific research on this topic. Points of view for rating of evidence in each category are based on consideration of cell culture and animal and human clinical data from the peer-reviewed scientific literature. A higher rating was given when there were both preclinical and clinical data, and there was consistency of findings among well-controlled human studies.

Regarding drug uses of the chemical capsaicin, the Food and Drug Administration's Center for Drug Evaluation and Research has determined it to be GRASE (generally recognized as safe and effective) as an external analgesic counterirritant when used as directed.⁶ Yet, in some cases, it can be a skin irritant, so care needs to be exercised by those with possible allergies to this plant.¹⁹⁴ Capsaicin is GRAS (generally recognized as safe) for use in cosmetic formulations that are not irritating.⁶ However, capsaicin is not GRAS for fever blister and cold sore treatment. When administered topically, capsaicin can enhance penetration of anti-inflammatory

agents, suggesting that caution should be exercised in using capsaicin-containing cosmetic products.

Capsicum fruit is GRAS by the US Food and Drug Administration's Center for Food Safety and Applied Nutrition for use in foods. Capsaicin is rapidly absorbed from the stomach and small intestine. It is then quickly metabolized in the liver by cytochrome P450 enzymes, which may limit systemic, pharmacological effects of enterally absorbed capsaicin.^{6,33,195}

Early preclinical and clinical studies evaluating the effect of feeding *Capsicum* on physiological and toxicological end points have been reviewed previously. In general, it was concluded that acute toxicity of capsaicinoids as a food additive in humans was negligible, in part because of the self-limiting sensory responses accompanying overconsumption.^{2,20} More recent studies indicate that paprika oleoresin elicited no adverse effects in chronic and subchronic toxicity and carcinogenicity studies.^{196,197} In a 26-week gavage study, the no-adverse-effect level of dihydrocapsaite was determined to be 1000 mg/kg per day for male and female rats. Capsiate was determined not to be teratogenic in rats and rabbits, not to be clastogenic, and to exhibit extremely low likelihood of inducing genotoxicity. Orally administered capsinoids were not detected in the systemic circulation of the animals.^{198–204} Healthy human volunteers ingesting a single oral dose of capsinoids (15 or 30 mg per person) obtained from CH-19 sweet pepper exhibited no adverse outcomes or

clinically significant changes in physical or biochemical outcome measures.²⁰⁴

There is a potential for drug-food interactions in light of capsaicin's capacity to affect the function and expression of p-glycoprotein and multidrug resistance-associated proteins.^{205,206} Of interest is that capsaicin and capsaicinoids inhibit cytochrome P450 3A4 in human liver microsomes in vitro.²⁰⁷ This is noteworthy, because P450 3A4 inhibition by dietary polyphenols has been known to inhibit the in vitro metabolism of clinical drugs.²⁰⁸ The clinical relevance of this finding with capsaicinoids, however, is unknown.

There have been anecdotal findings and data from small studies that red pepper consumption may be associated with adverse gastrointestinal effects and rectal hypersensitivity.^{55,56,209–211} A recent prospective, randomized, placebo-controlled, double-blind, crossover trial involving 43 subjects found that consumption of red pepper powder (3.0 g/d) exacerbated symptoms of acute anal fissures.²¹⁰

There are reports of arterial hypertensive crisis following acute ingestion of chili peppers,^{212–214} and one observation that use of a topical capsaicin patch can lead to coronary vasospasm and acute myocardial infarction.²¹⁵ The acute effects of dihydrocapsaicin and capsaicin on white blood distribution and any subsequent changes in the effectiveness of the immune response in rats deserve further evaluation.²¹⁶ The prevalence of and basis for these adverse events warrant further scrutiny.

Although few concerns about potential toxicity in humans have been identified in short-term feeding studies, long-term consequences of red pepper and capsaicinoid intakes in humans need to be more clearly evaluated. In particular, future human trials examining the impact of capsaicinoids, capsinoids, and red pepper consumption on health end points need to better characterize the effects of dose, form, and duration of intake.

Summary

Capsaicin has a demonstrated benefit as a topical pharmaceutical to mitigate pain and other neurological conditions. The capacity of dietary capsaicin to manage gastrointestinal distress is unclear, because of lack of understanding of its apparent contradictory actions within various segments of the gastrointestinal tract. More promising are data linking capsaicin and red pepper to improving weight loss and weight maintenance, as well as lessening glucose intolerance and insulin resistance. Moreover, use of the less-pungent capsates from sweet pepper cultivars may open up avenues for application of these nonpungent *Capsicum*

components to health promotion strategies without limitations associated with poor compliance. However, progress in substantiating benefits in these areas is limited by the need for larger, well-controlled human studies that can characterize capsaicin/red pepper at doses more consistent with typical human intakes. Furthermore, the contributions to variability in outcomes due not only to dose, but also to length of red pepper exposure, specific dietary protocols, subject characteristics, and genetic aspects of responsiveness, need to be more thoroughly defined. Likewise, insights into both TRPV1-associated and TRPV1-independent mechanisms for any health benefits of dietary red pepper have only begun to be explored.

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