

# Pharmacological activity of capsaicin: Mechanisms and controversies (Review)

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**Abstract.** Capsaicin, which is abundant in chili peppers, exerts antioxidative, antitumor, antiulcer and analgesic effects and it has demonstrated potential as a treatment for cardiovascular, gastrointestinal, oncological and dermatological conditions. Unique among natural irritants, capsaicin initially excites neurons but then ‘calms’ them into long-lasting non-responsiveness. Capsaicin can also promote weight loss, making it potentially useful for treating obesity. Several mechanisms have been proposed to explain the therapeutic effects of capsaicin, including antioxidation, analgesia and promotion of apoptosis. Some of the mechanisms are proposed to be mediated by the capsaicin receptor (transient receptor potential cation channel subfamily V member 1), but some are proposed to be independent of that receptor. The clinical usefulness of capsaicin is limited by its short half-life. The present review provided an overview of what is known about the therapeutic effects of capsaicin and the mechanisms involved and certain studies arguing against its clinical use were mentioned.

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## 1. Introduction

The chili pepper *Capsicum annuum* L., which belongs to the family *Solanaceae* in the class *Magnoliopsida*, is an annual or limited perennial herb widely used globally as a medicinal and edible plant. The fruit is used in the traditional medicines of China and other countries for warming the body, ‘dispelling cold’ and promoting digestion. The fruit contains various active components, including capsaicin, which is the most abundant pungent compound; capsaicinoids and carotenoids (1). Capsaicin, in turn, exists as a family of compounds including capsaicin, dihydrocapsaicin, homocapsaicin, homodihydrocapsaicin, nordihydrocapsaicin, capsaicin esters, dihydrocapsaicin esters, nordihydrocapsaicin esters, capsanthin- $\beta$ -D-glucoside and dihydrocapsanthin- $\beta$ -D-glucoside (2) (Fig. 1). Capsaicin exerts analgesic, antioxidant, cardioprotective, anticancer and thermogenic effects, and it can promote weight loss (3). Some of these effects are mediated by the receptor called ‘transient receptor potential cation channel subfamily V member 1’ (TRPV1), to which capsaicin binds specifically. Some evidence suggests that capsaicin may inhibit signal transducer and activator of transcription 3 (STAT3), but the minimal concentration needed to inhibit STAT3 (50 M) is substantially higher than the concentration required to stimulate TRPV1 (1-5 M) (4,5).

## 2. Structure and physicochemical properties of capsaicin

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide, C<sub>18</sub>H<sub>27</sub>NO<sub>3</sub>) is a colorless lipophilic crystalline substance (Fig. 2). It is an amide that forms through condensation of vanillylamine and caprylic acid. It has a melting point of 65°C and a boiling point of 210-220°C and it is highly soluble in ethanol, ether, benzene and chloroform, but only slightly soluble in carbon disulfide. The capsaicin structure can be divided into an aromatic ring (Fig. 2A), amide bond (Fig. 2B) and hydrophobic side chain (Fig. 2C). The various members of the capsaicin family differ from capsaicin mainly in the substitutions on the aromatic ring and hydrophobic side chain (Fig. 1) (6,7). The substituents at positions 3 and 4 on the aromatic ring (Fig. 1) are important active groups. The phenolic hydroxyl group at position 4, for example, acts as a hydrogen bond donor or acceptor in capsaicin agonists; substitution of this hydroxyl group for a

hydrophobic group can increase capsaicin activity. Whether the hydrophobic side chain is a saturated or unsaturated alkyl chain, substituted naphthyl group, or something else can influence the activity of capsaicin (8,9).

### 3. Pharmacological effects of capsaicin

**Antioxidant effects.** Capsaicin has been revealed to inhibit lipid peroxidation in red blood cell membranes as well as in the liver and mitochondria of mice, and it can block the peroxidation of low-density lipoproteins in humans (10,11). In fact, the antioxidant activity of capsaicin exceeds that of vitamin E in some cases (12). The levels of capsaicin in food can alleviate oxidative stress and increase cellular antioxidant capacity by preventing reactive oxygen species from oxidizing glutathione (13). Capsaicin can reverse the ability of high blood cholesterol levels to inhibit the antioxidant enzymes glutathione reductase, glutathione transferase and superoxide dismutase (14,15). Capsaicin can also scavenge free radicals such as 1,1'-diphenyl-2-picrylhydrazyl (DPPH) (13). Other members of the capsaicin family, such as dihydrocapsaicin and 9-hydroxycapsaicin, appear to have antioxidant activity similar to that of capsaicin (16).

In capsaicin and other members of the family, the benzene ring and the substituents of the benzene ring appear to be important for antioxidant activity. The benzene ring of capsaicin may interact with the benzene ring of DPPH, while the methoxy and hydroxy substituents at the ortho position of the benzene ring can strongly influence antioxidant activity (13).

Adults who received capsaicin for 4 weeks demonstrated lower levels of oxidation of serum lipoproteins (17). In mitochondria, capsaicin can reduce lipid peroxidation and, more generally, oxidative stress. It can alleviate ischemia-reperfusion injury in myocardium and kidney. Most of these antioxidant effects appear to be mediated by TRPV1 (18). The search continues for capsaicin analogues with even stronger antioxidant activity.

**Analgesic effects.** TRPV1 is a  $\text{Ca}^{2+}$ -selective member of the family of transient release potential ion channels, which sense heat. TRPV1 in the prelimbic and infralimbic cortex has also been revealed to mediate neuropathic pain. TRPV1 is broadly distributed in tissues of the brain, bladder, kidneys, intestines, epidermal keratinocytes, glial cells, liver, polymorphonuclear granulocytes, mast cells and macrophages (19).

Capsaicin is an agonist of TRPV1 that reduces its activation threshold. Uniquely, after TRPV1 has been activated by capsaicin, the receptor enters a long-lasting refractory state, in which it does not respond to mechanical pressure, pain or inflammatory agents (20). This so-called 'defunctionalization' results from the closing of the channel pore due to conformational changes that depend on extracellular  $\text{Ca}^{2+}$ . To what extent this transient 'defunctionalization' explains the observed analgesic effects of capsaicin remains unclear (21).

When activated by capsaicin, TRPV1 mediates  $\text{Ca}^{2+}$  influx and glutamate release, which may damage cutaneous autonomic nerve fibers and sensory nerve endings, decreasing pain sensation. In adult rats, the capsaicin analogue resiniferatoxin damages TRPV1-expressing myelinated nerve fibers and eliminates TRPV1-expressing unmyelinated nerve fibers, reducing perception of thermal pain.

The US Food and Drug Administration has approved capsaicin as an 8% dermal analgesic patch (640 mcg/cm<sup>2</sup>, total dose 179 mg), while lower doses do not relieve pain effectively (22). The 8% patch has proven safe and effective in controlling neuropathic pain resulting from post-herpetic neuralgia, post-surgical neuralgia, post-traumatic neuropathy, polyneuropathy and mixed pain syndrome (23). In a previous trial (24), capsaicin markedly reduced pain attacks, prolonged sleep duration and improved sleep quality, while reducing dependence on opioids and antiepileptics. ~10% of patients in that trial reported adverse drug reactions, the most frequent of which were erythema and pain at the application site. In a different study including two clinical trials, it has been suggested that the 8% patch is effective against HIV-associated distal sensory polyneuropathy (25).

Adlea, a highly purified form of capsaicin, has exhibited analgesic efficacy in clinical trials involving patients with intermetatarsal neuromas, lateral epicondylitis or end-stage osteoarthritis. A trial is ongoing to assess the safety and efficacy of the drug for patients undergoing total knee arthroplasty (23,26).

N-palmitoyl-vanillamide, also called palvanil, is also present in *Capsicum* but at markedly lower levels than capsaicin. Palvanil has demonstrated analgesic potential while inducing smaller fluctuations in body temperature and bronchoconstriction than capsaicin. It also exerts the analgesic effects through TRPV1, activating the receptor more slowly and defunctionalizing it more completely than capsaicin does (27).

**Antitumor effects.** Similar to numerous other dietary phytochemicals, capsaicin shows antitumor activity. It alters the expression of several genes that arrest the cell cycle in tumor cells and promotes apoptosis. These effects have been demonstrated in colon adenocarcinoma, pancreatic cancer, hepatocellular carcinoma, prostate cancer, breast cancer and numerous other types of cancer (Table I), without damage to normal cells. The way capsaicin exerts these effects is only beginning to emerge and the mechanisms appear to involve accumulation of intracellular  $\text{Ca}^{2+}$ , generation of reactive oxygen species, disruption of mitochondrial membrane potential and upregulation of the transcription factors NF- $\kappa$ B and STATS. Capsaicin has been revealed to act through TRPV1 to promote apoptosis of numerous types of cancers. Whether it also acts through other TRPVs, such as TRPV6 in prostate cancer, remains to be clarified (28,29).

**Weight-lowering effects.** Capsaicin causes TRPV1 to stimulate the release of catecholamine from catecholaminergic neurons in the rostral ventrolateral medulla of the brain, thereby promoting weight loss (30). It upregulates adiponectin and other adipokines to reduce fat accumulation in obese mice. Capsaicin has been shown to decrease appetite (31). When delivered as part of a high-fat diet, it increases thermogenesis and lipid oxidation, while also reducing levels of fasting glucose and plasma triglycerides, which suggests therapeutic potential for obesity-related diseases such as insulin resistance and type 2 diabetes mellitus (32,33). Indeed, studies of various capsaicin doses in obese mice have suggested that it can partially reverse obesity-induced glucose intolerance by suppressing inflammatory responses and enhancing fatty acid oxidation in adipose tissue and liver (34).

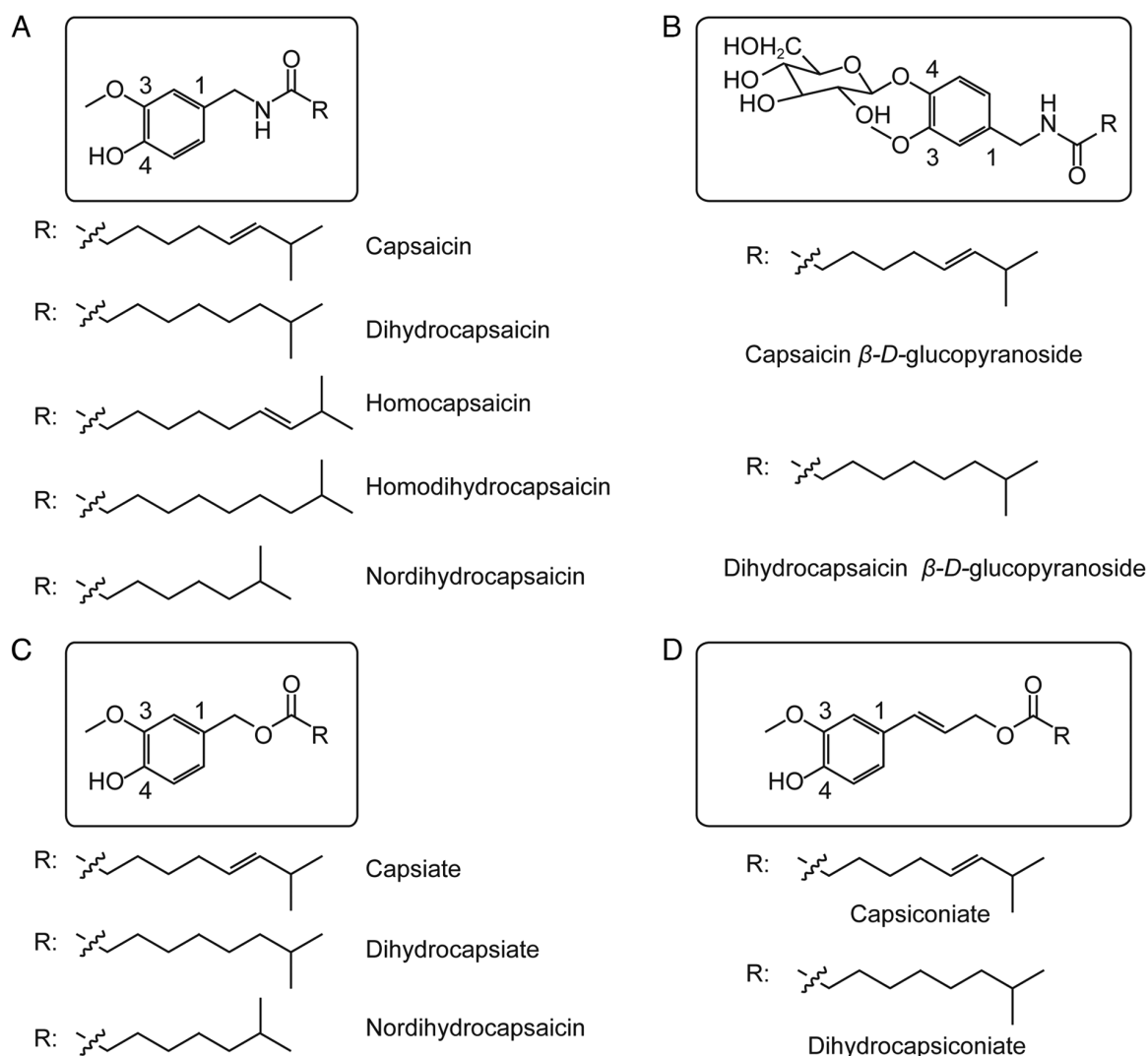


Figure 1. Chemical structures of capsaicins and capsaicin esters. (A) Capsaicin and its analogues; (B) capsaicin glucopyranoside and dihydrocapsaicin glucopyranoside; (C) and (D) capsiate and its analogues.

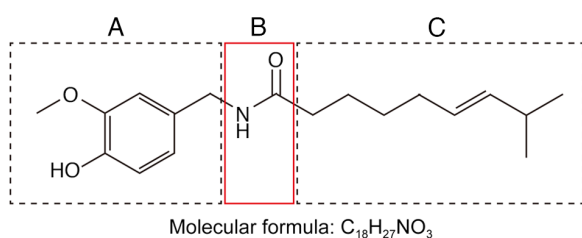


Figure 2. Functionally important subdivisions of the capsaicin structure: (A) Aromatic ring, (B) amide bond and (C) hydrophobic side chain.

On the other hand, certain studies (35,36) have failed to detect any effect of capsaicin on energy expenditure or lipid oxidation. While the absence of these effects may be real, it may also be an artifact of administering too little capsaicin for a short period of time, or the thermogenic effects may be too subtle to detect in the relatively small animal groups and short measurement periods in those studies.

The available evidence suggests that capsaicin lowers lipid levels by altering intestinal permeability and the gut microbiome, in turn influencing the gut-brain axis (37) (Fig. 3).

Future studies are needed to verify and elucidate the molecular pathways involved.

**Gastrointestinal effects.** In rats and guinea pigs, TRPV1 is expressed and active within the myenteric ganglia and inter-ganglionic fiber tracts that extend throughout the gastrointestinal tract, including the muscle layers, blood vessels and mucosa within the tract (38). TRPV1 is also expressed outside the gastrointestinal nervous system, such as in gastric epithelial cells, in which it stimulates the secretion of gastrin (39).

Previous studies have attributed several positive gastrointestinal effects to capsaicin: It induces the release of calcitonin gene-related peptide, activates gastroprotective cyclooxygenase-1 and increases the absorptive surface of the small intestine by lengthening and thickening microvilli and by altering the permeability of the brush border membrane, in turn increasing zinc absorption (40-42). In non-alcoholic fatty liver disease, dietary capsaicin has been revealed to promote hepatic phosphorylated hormone-sensitive lipase, carnitine palmitoyltransferase 1 and peroxisome proliferator-activated receptor  $\delta$  (43).

Table I. Reported antitumor effects of capsaicin in animal models.

Animal model	Capsaicin treatment		Results
	Dose	Regime	
BALB/cJ and BALB/cJ nu/nu mice injected with CT26 tumor cells	100-200 $\mu$ g	Intratumoral on days 5, 10 and 15	Reduced tumor growth
BNX nu/nu male mice injected with PC-3 cells	5 mg/kg	Gavage 3 days per week for 4 weeks	Reduced tumor growth
Athymic nude mice injected with PC-3 cells	5 mg/kg	Subcutaneous injection every two days for 14 days	Reduced tumor growth and induced apoptosis
Female athymic nude mice injected subcutaneously with AsPC-1 tumor cells	2.5 mg/kg	Five times a week	Reduced tumor growth without adverse effects
Male athymic nu/nu mice injected with U266 cells	5 mg/kg	Three times a week	Reduced tumor growth
Male athymic nude mice injected subcutaneously with T24 cells	1 mg/kg	Twice a week for 3 weeks	
Female triple deficient beige/nude/xid mice injected with MDA-MB231 cells	5 mg/kg	Subcutaneous injection every 3 days for 4 weeks	Reduced tumor growth by 50%
Male nude mice injected subcutaneously with H69 cells	5 mg/kg	Oral gavage 3 days per week for 4 weeks	Reduced tumor growth
	10 mg/kg	Solid diet until tumors of control group reached 2,000 mm <sup>3</sup>	
Female BALB/c athymic nude mice injected subcutaneously with Colo 205 cells	1 or 3 mg/kg	Intraperitoneal injection once daily for 4 weeks	Reduced tumor growth
Female athymic nude mice injected subcutaneously with AsPC-1 tumor cells	2.5 mg/kg	Orally fed 5 days a week for 6 weeks	Reduced superoxide dismutase activity in tumors by 60%, while increasing the ratio of oxidized to reduced glutathione
Male BALB/c (nu/nu) athymic nude mice injected subcutaneously with PANC-1 cells	5 mg/kg	Gavage 3 days per week for 4 weeks	Reduced tumor growth

On the other hand, a number of studies have suggested that prolonged exposure to high doses of capsaicin can harm the gastrointestinal tract. Thus, exploring the minimum effective doses required to achieve the desired therapeutic effects and minimizing the potential side effects are quite necessary for enhancing the clinical utility of capsaicin-based treatments. TRPV1 activation induces release of substance P, which can drive gastrointestinal inflammation (44). In addition, TRPV1 is upregulated in irritable bowel syndrome and appears to contribute to the gastrointestinal hypersensitivity and pain associated with the condition (22,45).

*Anti-neurodegenerative effects.* Capsaicin has demonstrated therapeutic potential in several animal models of Alzheimer's disease (AD). It can partially reverse streptozotocin-induced biochemical and behavioral changes that mimic AD (46). In the APP/PS1 mouse model, capsaicin reduced the formation of amyloid fibrils from amyloid precursor protein. In a third AD model (47), capsaicin substantially ameliorated synaptic

damage and tau hyperphosphorylation induced by cold water stress. Further studies should explore the therapeutic potential of dietary capsaicin for treating and possibly even preventing AD (48).

In an animal model of Parkinson's disease based on lipopolysaccharide-induced inflammation, capsaicin appeared to activate TRPV1 in M1/M2 dopaminergic neurons, which may alleviate neuro-inflammation and oxidative stress from activated glia (49). The beneficial effects of capsaicin and TRPV1 were confirmed in these studies using appropriate antagonists (50). Future studies should continue to explore the potential of capsaicin for treating Parkinson's disease and should elucidate the mechanisms involved.

*Dermatological effects.* TRPV1 is expressed in human keratinocytes. Although activation of epidermal TRPV1 induces the release of inflammatory factors, capsaicin downregulates hypoxia-inducible factor-1 $\alpha$  in psoriatic epidermis, slowing epidermal proliferation (51). It also

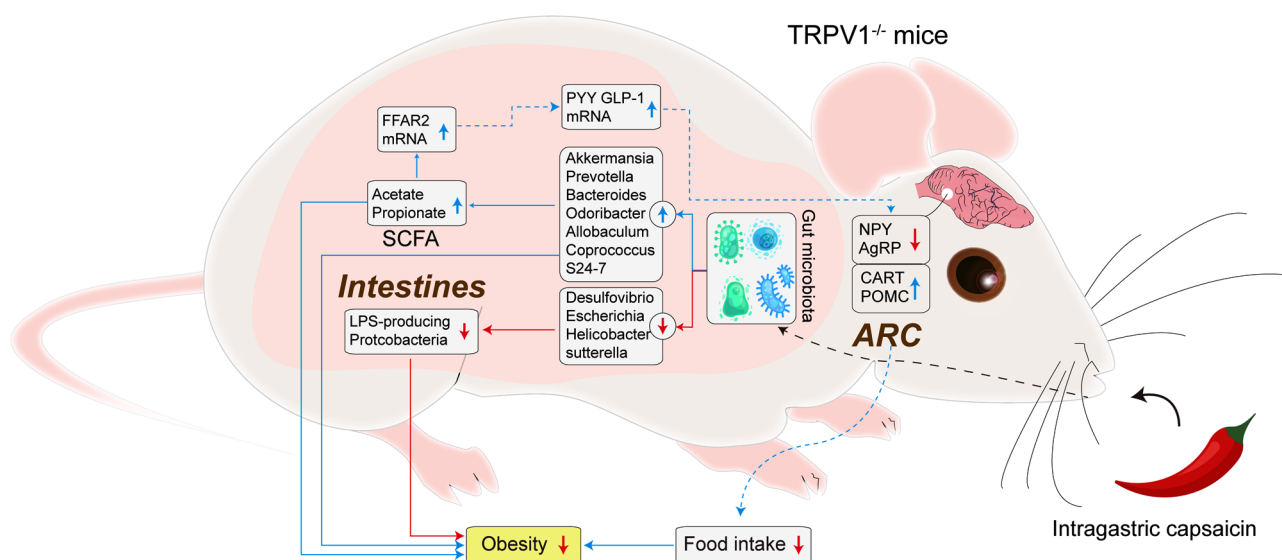


Figure 3. Potential pathways through which capsaicin may mitigate obesity in mouse models. AgRP, agouti-related peptide; ARC, arcuate nucleus; CART, cocaine- and amphetamine-regulated transcript; GLP-1, glucagon like peptide-1; LPS, lipopolysaccharide; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PYY, peptide YY; SCFA, short-chain fatty acids.

mitigates itching mediated by histamine, substance P and proteinase activated receptor-2. On the other hand, previous studies have failed to detect therapeutic effects of capsaicin against hemodialysis-induced pruritis, idiopathic intractable pruritis and notalgia paresthetica (52,53). In fact, an animal study linked capsaicin to the development of chronically relapsing pruritic dermatitis, which was associated with an elevated number of mast cells and hyperproduction of immunoglobulin E (54,55).

**Cardiovascular effects.** TRPV1 is expressed in the sensory nerves in cardiovascular structures, near the epicardium and in vascular endothelial cells (56). When blood flow to myocardium is reduced, such as during myocardial infarction, free oxygen radicals are produced, which activate TRPV1 (57). Myocardial injury also upregulates 12-hydroperoxyeicosatetraenoic acid, a metabolite of 12-lipoxygenase arachidonic acid that may bind to TRPV1 (58). Activation of the receptor may exert cardio-protective effects, leading to smaller infarcts and milder ischemic/reperfusion injury (59).

TRPV1 in the vasculature can promote vasoconstriction or vasodilation, depending on the situation. In the case of vasoconstriction, TRPV1 activation results in the release of substance P, which binds to neurokinin 1 (60,61). In the case of vasodilation, TRPV1 activation results in the release of calcitonin gene-related peptide or of protein kinase A and nitric oxide synthase (62,63). In both cases, TRPV1 activation leads to an increase in intracellular  $\text{Ca}^{2+}$  (64,65).

Capsaicin inhibits platelet aggregation, potentially by altering the fluidity of the platelet membrane. This mechanism appears to be independent of TRPV1 because the effects are not inhibited by a competitive TRPV1 inhibitor. On the other hand, capsaicin has also been shown to promote platelet aggregation through a mechanism dependent on TRPV1 (66-69). In that mechanism, TRPV1 may induce release of serotonin to drive platelet activation in response to adenosine diphosphate and thrombin (70-74).

#### 4. Pharmacokinetics of capsaicin

Numerous studies have indicated a relatively short half-life of capsaicin in various parts of the organism, including liver, kidney, intestine, lung and blood, restricting its clinical use (75). Within the organism, most capsaicin is metabolized in the liver, where it appears to be metabolized faster in microsomes than in the S9 fraction (76,77). The most abundant metabolites produced in liver microsomes are 16-hydroxycapsaicin, followed by 16,17-dehydrocapsaicin; the most abundant metabolites produced in the S9 fraction are different but have not been definitively identified (78). A number of experiments suggested that P450 enzymes can oxidize capsaicin to generate free radical intermediates (79-81). Further studies should clarify the metabolites of capsaicin in the liver, since some of the discrepancies reported so far may reflect different dosing conditions (82,83).

Capsaicin in the body diffuses into intestinal tissues, the jejunum and serosal fluid (84). A previous study has suggested that capsaicin and dihydrocapsaicin are absorbed to a greater extent by the jejunum and ileum than by the stomach (85).

Capsaicin is metabolized only slowly on the skin, where the main metabolites are vanillylamine and vanillic acid. It penetrates the skin with first-order kinetics. These characteristics make topical administration of capsaicin effective (86,87).

Capsaicin is widely used worldwide, but there is ongoing debate about the safety. For example, epidemiological and laboratory data have suggested that capsaicin can act as a carcinogen or anticarcinogen (88-90). Capsaicin appears to interact with xenobiotic-metabolizing enzymes, particularly microsomal cytochrome P450-dependent monooxygenases, which are involved in activation as well as detoxification of various chemical carcinogens and mutagens (1,91,92). The Indian population consumes several-fold more chili than populations in other countries, yet this does not appear to adversely affect growth, organ weight, nitrogen balance or blood chemistry (93). Previous studies in animals and mammalian cell lines have not suggested any mutagenic effects of capsaicin in

somatic cells or the germline (94). Capsaicin cream has been used in the clinic for numerous years to relieve various types of pain, and long-term local application of capsaicin can be effective for treating skin cancer in mice (28,50,95-98).

Although animal studies have indicated few or no side effects of capsaicin, it can irritate the skin of humans and excessive ingestion can cause nausea, vomiting, abdominal pain and burning diarrhea (99). Contact of capsaicin with eyes can cause severe tearing, pain, conjunctivitis, eyelid spasms and it can trigger mucosal irritation leading to serious gastritis and diarrhea. Loading capsaicin into nanoparticles may reduce these adverse effects while improving its efficacy by counteracting its hydrophobicity and prolonging its half-life in the circulation (100,101). Combining capsaicin with other phytochemicals may also mitigate the side effects (102-104); these compounds may include vanilloids, flavonoids, alkaloids, terpenoids, terpenyl phenols, fatty acids, cannabinoids and sulfur-containing compounds. Furthermore, different individuals have different intolerance to capsaicin, personalized treatment programs are needed. Therefore, capsaicin products should be used carefully in light of the range of pharmacological activities and potential for adverse effects; meanwhile, further research is needed to assess the safety of prolonged capsaicin exposure (105).

## 5. Conclusion

In addition to being widely used as a local analgesic, capsaicin has also demonstrated antioxidant, anticancer, antiobesity and gastroprotective activities. The longer half-life of capsaicin in the lungs and skin implies that it may have stronger effects in these tissues. Systemic administration of capsaicin seems unlikely to be effective because of its metabolic instability and short half-life in the circulation. Further efforts to develop capsaicin analogues and nanoparticles delivery system may succeed in prolonging half-life while also increasing efficacy, making it an effective analgesic against numerous diseases.

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## Availability of data and materials

Not applicable.

## Authors' contributions

XS and WZ conceived and designed the study. YZ, JF and ZF analyzed the data. XS wrote the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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