Unlocking the potential of capsaicin in oral health (Review)

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Abstract. Capsaicin is a bioactive compound found prominently in *Capsicum annuum* L. plants and takes on a pivotal role in their characteristic spiciness. Previous studies have delved into the potential analgesic effect of capsaicin in various oral conditions, such as oral neuropathic pain, trigeminal neuralgia, oral mucositis, temporomandibular joint disorders and burning mouth syndrome. Capsaicin has also demonstrated promise in inhibiting the proliferation of different oral cancer cell lines. Its antimicrobial properties have also been shown to inhibit the growth of oral pathogens associated with dental caries, periodontitis and oral candidiasis. However, to harness its benefits effectively, more studies are required to establish optimal dosages for pain relief while minimizing adverse effects. In addition, investigation of the effect of capsaicin on nonpathogenic oral bacteria and viruses is warranted. Human-based research is crucial for elucidating the biomolecular mechanisms underlying the properties of capsaicin, potentially leading to the development of more effective interventions for oral health problems.

Contents

1. Introduction

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a bioactive compound of considerable importance among natural constituents found in *Capsicum* plants (1-3). Capsaicin, present in the *Capsicum annuum* L. plant, imparts the characteristic spiciness to this species. This plant is a member of the Solanaceae family, which is one of the earliest cultivated crops in the Western hemisphere (4). The growing societal consumption of *Capsicum annuum* is underscored by its substantial nutritional value, which serves as a rich source of essential vitamins such as C, E and provitamin A (carotene), renowned for their antioxidant properties (5). In addition, it offers a plentiful supply of neutral phenolic compounds, including luteolin, quercetin and capsaicinoids (6,7).

Capsaicin is acknowledged for its potential analgesic properties and therapeutic applications in the management of inflammation and inflammatory diseases. The underlying mechanism predominantly centers on the interaction between capsaicin and its receptor, transient receptor potential vanilloid 1 (TRPV1). Its molecular basis was elucidated by Caterina *et al* (8) in 1997, igniting significant interest in manipulating capsaicin and its receptor pharmacologically (9). Clinical studies have explored capsaicin as a topical treatment for various pain conditions, such as osteoarthritis, rheumatoid arthritis, postherpetic neuralgia, psoriasis, and diabetic neuropathy (10,11).

Furthermore, capsaicin exhibits *in vitro* antibacterial activity against a spectrum of pathogens, such as *Streptococcus pyogenes* (12), *Porphyromonas gingivalis* (13), *Vibrio cholerae* (14) and *Staphylococcus aureus* (15,16), reflecting its potential in the treatment of pathogenic bacterial infections and alleviation of antimicrobial resistance. In addition, capsaicin has exhibited promise as a chemopreventive agent for cancer. Its combination with radiotherapy and chemotherapy drugs shows the potential to enhance patient sensitivity to these treatments, reduce required dosages and improve overall tolerance to cancer therapy (17,18).

The multifaceted attributes of capsaicin, encompassing its analgesic, anti-inflammatory, antimicrobial and anticancer properties, hold significant promise in an oral health context. This review aimed to explore relevant publications that investigate the utilization of capsaicin as a therapeutic agent for oral conditions and the preservation of oral well-being.

2. Capsaicin biosynthesis

The biosynthesis pathway of capsaicin (Fig. 1) involves two distinct routes: i) Through the synthesis of vanillylamine via the phenylpropanoid shikimate/arogenate pathway; and ii) through the branched fatty acid derived from

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valine (19-21). Key enzymes proposed to participate in the phenylpropanoid pathway include phenylalanine ammonia lyase, cinnamate 4-hydroxylase, 4-coumaroyl-CoA ligase, coumarate 3-hydroxylase, hydroxycinnamoyl transferase, caffeoyl-coenzyme A (CoA) O-methyltransferase, hydroxycinnamoyl-CoA hydratase/lyase, putative aminotransferase and acyltransferase (21-26). For the mechanisms underlying the synthesis of branched-chain fatty acids, studies have hypothesized that a desaturase is involved in the conversion of 8-methylnonanoic acid into 8-methyl-6-nonenoic acid (24,27). Mazourek *et al* (21) proposed the inclusion of the biosynthesis of amino acids that leads to capsacinoids in the branched-chain fatty acid biosynthetic pathway.

Researchers have employed various techniques to manipulate culture strategies and thus enhance capsaicinoid biosynthesis. Among these strategies, osmotic stress has become an effective method, resulting in the highest product accumulation, followed by precursor feeding (20). In addition, the duration of exposure to these treatments significantly influences the level of capsaicin biosynthesis (20).

3. Analgesic and anti-inflammatory properties

Studies have comprehensively elucidated the foundational mechanism underlying the analgesic and anti-inflammatory properties of capsaicin (Fig. 2), whereby capsaicin selectively interacts with the TRPV1 cation channel (28). This channel exhibits high permeability to calcium (Ca^{2+}) ions and detects potentially noxious stimuli. This interaction results in the opening of Ca^{2+} channels and the subsequent neurotransmitter release. This calcium-dependent process culminates in the depletion of substance P and desensitization of primary afferent fibers to painful stimuli, inducing analgesia (28). Concurrently, capsaicin exhibits anti-inflammatory properties by reducing proinflammatory cytokines and vascular permeability (29). Capsaicin can deactivate nuclear transcription factor κB, thereby inhibiting prostaglandin E-2 and nitric oxide production, subsequently attenuating vascular leakage and modulating inflammatory cell migration mediated by tumor necrosis factor-α and interleukin (IL)-1 (30).

Orofacial neuropathic pain. Capsaicin is commonly administered topically to treat chronic pain associated with osteoarthritis, rheumatoid arthritis, diabetic neuropathy and nondiabetic peripheral neuropathy (10,31). The pain-relieving effects of low-dose topical capsaicin (0.025, 0.050 and 0.075%) were also demonstrated in conditions such as oral neuropathic pain and trigeminal neuralgia (32-34). These capsaicin cream formulations are also available over the counter (35). However, the efficacy of lower doses appears to be moderate and patient compliance with this therapy is often hindered by the need for daily repetitive application and the potential for irritation, which can manifest as sensations of burning, stinging or itching (31,36). Therefore, products containing higher concentrations of capsaicin were suggested to relieve pain after a single topical application (37). Higher capsaicin doses may desensitize cutaneous and subcutaneous receptors, resulting in reduced responsiveness to various sensory stimuli (3).

Several studies have tested the effectiveness of 8% capsaicin patch in managing orofacial neuropathic pain. In a case report, Sayanlar *et al* (38) revealed that a single application of the 8% capsaicin topical patch on a patient diagnosed with trigeminal postherpetic neuralgia demonstrated a substantial effect on reducing the pain level and area. Gaul and Resch (39) reported the effectiveness and safety of the application of 8% capsaicin patch in the treatment of four cases of neuropathic pain in the head and facial region caused by surgery or herpes zoster infection. Sustained reduction in pain was noted in three of the patients; however, two of them required repeated applications of capsaicin (39). Similarly, Martinez *et al* (40) reported the success of repeated applications of 8% capsaicin patch in managing pain in two patients with trigeminal neuralgia. These three studies have used a similar method, which was applying 8% capsaicin for 60 min in the painful area and ensuring eye protection such as using safety goggles, a compress and plaster, and eye dressing and cream (38-40).

Burning mouth syndrome (BMS) is a chronic neuropathic pain common in post-menopausal women (41). Several studies have explored the effectiveness of capsaicin in managing BMS symptoms using capsaicin therapies in different durations (ranging from 1 month to 1 year), concentrations (0.01, 0.02, 0.025 and 0.25%), and forms (capsule, gel and mouth rinse). All of these studies have reported that capsaicin successfully relieved BMS-related pain and discomfort (42-45). A study found no significant difference in the effectiveness of 0.01 and 0.025% capsaicin gels in reducing BMS symptoms, which indicates that the 0.01% gel is adequate to activate the analgesic effect of capsaicin for BMS (44).

Oral ulcers. Capsaicin in chili peppers was once proposed as a component that could cause ulcers, particularly in the gastrointestinal tract (46,47). However, later studies have found that it acted contrarily, i.e., capsaicin helps in preventing and relieving ulcers by inhibiting gastric acid secretion and stimulating mucus secretions and blood flow (47).

Despite studies discussing the effect of capsaicin on gastric or intestinal ulcers, published studies involving capsaicin and oral ulcers are limited. A study on 11 patients who underwent chemotherapy or radiotherapy reported the significant analgesic effect of orally administered capsaicin on oral mucositis pain; however, the effect was temporary in most patients (48). In an animal study, Jiang *et al* (49) reported a healing rate of 97.8% on the oral ulcer model in rats after 7 days of treatment with 0.05% capsaicin candy, which was significantly higher than those in groups receiving a placebo and dexamethasone. The study also reported a high inflammatory effect of capsaicin, as it reduces the expression of TNF-α and IL-6 (49). This finding holds significance in the treatment of oral ulcers and needs further investigation.

Temporomandibular disorders (TMDs). TMDs are considered neuropathic and idiopathic pain disorders (50,51). In a randomized controlled study involving 30 patients with unilateral pain in the temporomandibular joint area, Winocur *et al* (52) found no significant difference in the pain relief effect between the group using 0.025% capsaicin cream four times a day and the placebo group, despite the significant improvement in pain parameters throughout the experiment (4 weeks). Later, Campbell *et al* (53) demonstrated that a higher concentration

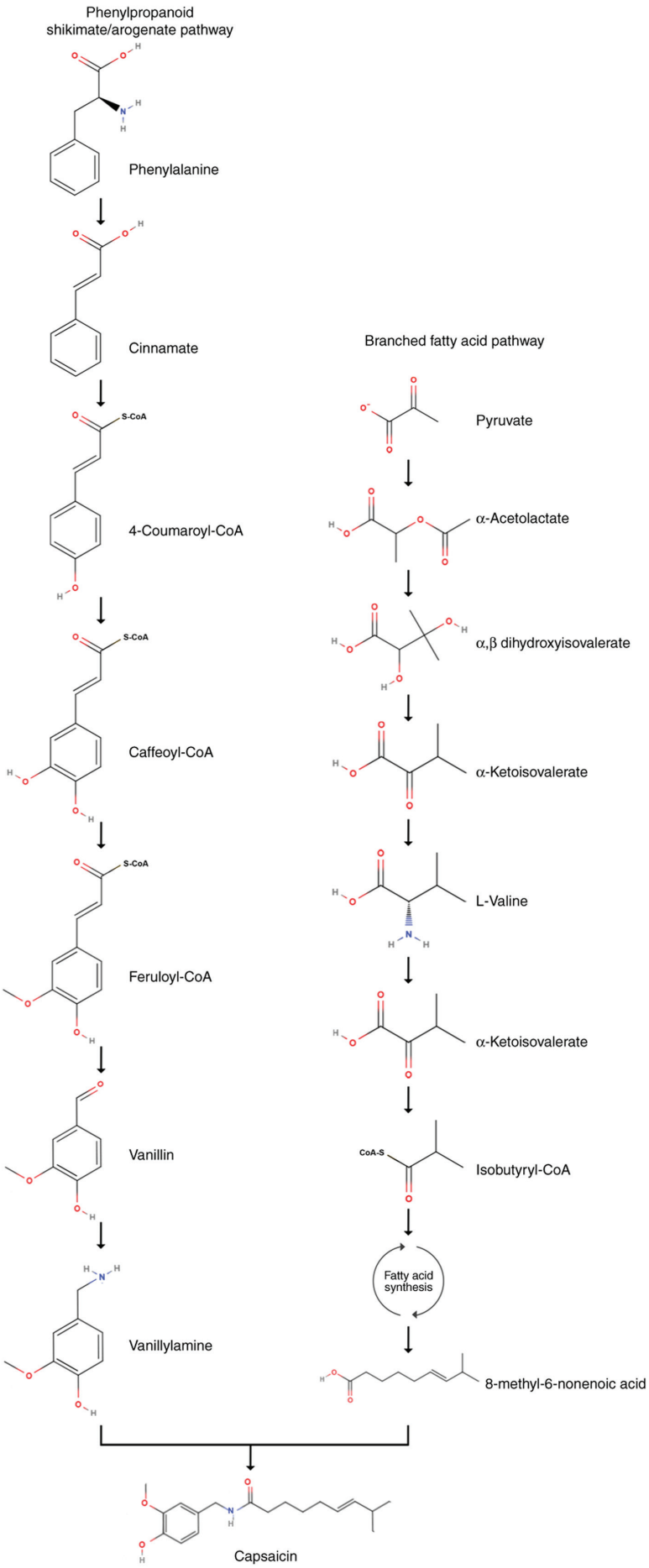

Figure 1. Capsaicin biosynthesis pathway. CoA, coenzyme A.

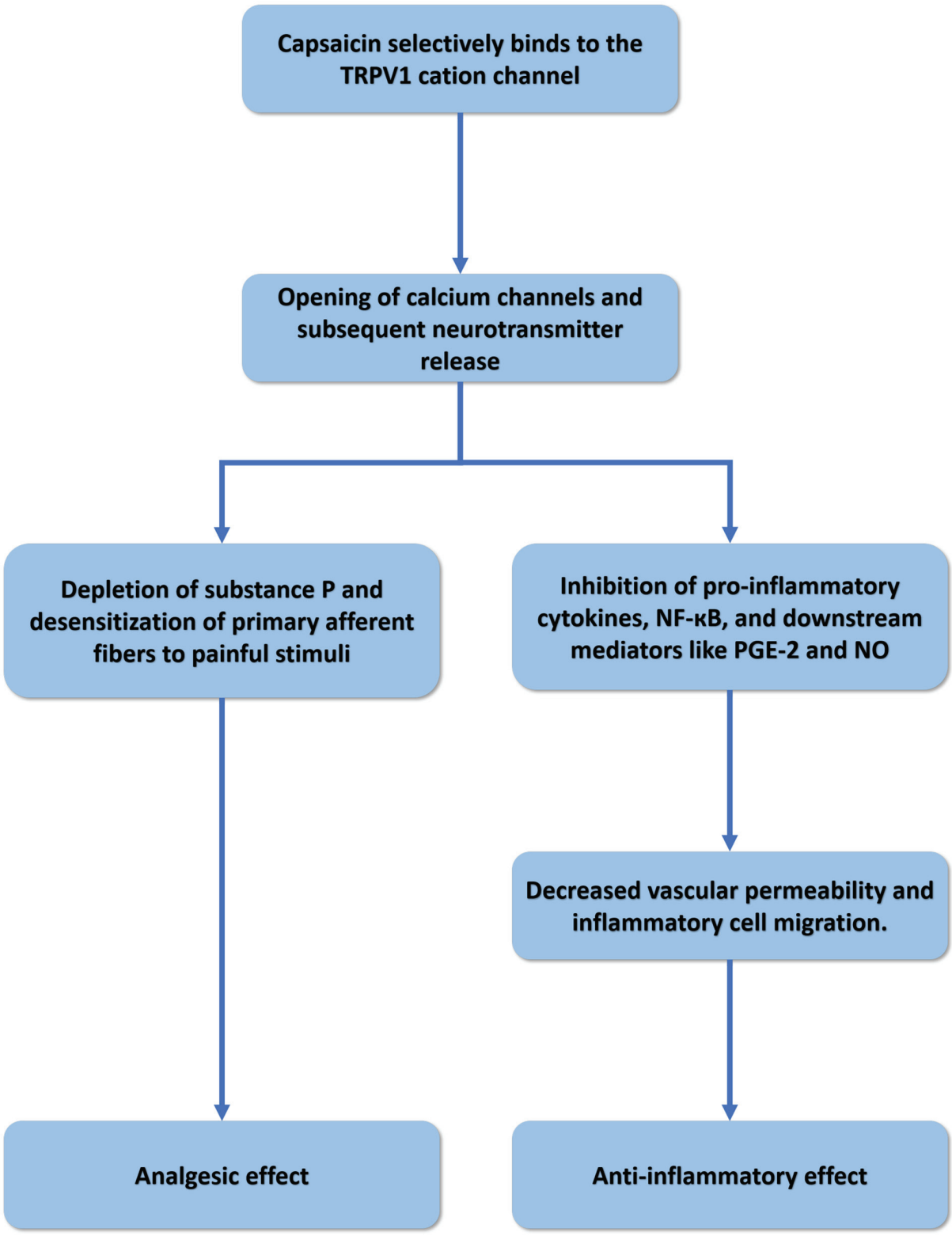

Figure 2. Mechanism of action of capsaicin on pain perception and inflammation (28-30). NO, nitric oxide, PGE, prostaglandin E; TRPV1, transient receptor potential vanilloid 1.

of capsaicin (8% cream) was effective in relieving pain in patients with TMDs, despite the shorter experiment duration (1 week). However, the authors also reported that the finding may be biased by the small sample size and inclusion of female subjects only due to funding and difficulty in participant recruitment (53).

4. Anticancer properties

In experimental studies utilizing cell cultures and animal models, capsaicin consistently demonstrated the capacity to inhibit oral cancer cell growth and induce apoptosis (54). Table I lists several *in vitro* and *in vivo* investigations that

Table I. Studies on capsaicin treatment for oral cancer.

Author(s), year	Cell line(s)/test species	Capsaicin treatment	Effects	(Refs.)
Tanaka *et al*, 2002	4-NQO-induced tongue tumorigenesis in four-week-old male F344 rats	Diets containing 500 ppm capsaicin for 10 and 28 weeks	Reduced incidence of carcinoma and severe dysplasia, as well as increased apoptotic index and proliferative index of squamous cell carcinoma	(55)
Ip *et al*, 2012	Human nasopharyngeal carcinoma (NPC-TW 039)	Various doses of capsaicin (0, 200, 250, 300 and 400 μM) for different incubation times (12, 24, 36 and 48 h)	Induced ER stress, increased ROS production, enhanced apoptosis induction with higher doses and longer incubation periods	(56)
Kamaruddin *et al*, 2019	Oral squamous cell carcinoma of Asian origin (ORL-48)	Various doses of capsaicin (50, 100, 150, 200, 250, 300 and 350 μM) for different incubation times (24, 48 and 72 h)	Induced apoptosis via disruption of mitochondrial membrane potential, activation of caspase-3, -7 and -9, intrinsic apoptotic pathway activation, lowest cell viability and highest apoptosis percentage with longer incubation periods	(57)
Mohamed and AlQarni, 2019	Experimentally induced buccal pouch carcinogenesis in five-week-old golden (Syrian) male hamsters	Water containing 10 ppm capsaicin for 9 weeks	Slower cell proliferation, reduced tumor aggressiveness and lower oral epithelial dysplasia	(58)
Chang *et al*, 2020	p53-mutated HSC-3 and p53-functional SAS cells	Different concentrations of capsaicin for 24 or 48 h; 2 mM capsaicin for 1 h incubation at the end of treatment	Induced both autophagy and apoptosis in p53-mutated HSC-3 cells, but only autophagy in p53-functional SAS cells	(59)
Huang *et al*, 2021	Oral squamous cell carcinoma (HSC-3 and SAS)	200 μM capsaicin for 30 min	Induced ER stress and autophagy by suppressing ribophorin II, increased sensitivity of cancer cells to chemotherapeutic agents, inhibited viability by increasing necroptosis markers (phospho-MLKL and phospho-RIP3)	(60)
Chakraborty *et al*, 2021	Oral cancer cells Cal 27	Capsaicin treatments ranged from 0 to 150 μM with a 24-h incubation time. Bacterial antigens, LPS and LTA, were introduced to cancer cells before and/or during capsaicin administration	Exposure to bacterial antigens resulted in reduced death and metabolic inhibition of cancer cells, as well as decreased SOCS3 gene expression, compared to capsaicin treatment alone	(61)

4-NQO, 4-nitroquinoline 1-oxide; ER, endoplasmic reticulum; ROS, reactive oxygen species; MKLK, mixed lineage kinase domain-like protein; RIP3, receptor-interacting protein kinase 3; LPS, lipopolysaccharide; LTA, lipoteichoic acid; SOCS3, cytokine signalling 3.

explored the potential of capsaicin as a treatment agent for oral cancer (55-61). The proposed mechanism underlying the anti-cancer activity of capsaicin on oral cancer from several studies is shown in Fig. 3 (54-61). Capsaicin exerts anti-proliferative effects on oral epithelial dysplasia, leading to a reduction in its incidence, severity and aggressiveness (55,58). Capsaicin disrupts the mitochondrial membrane potential in oral squamous cell carcinomas by triggering endoplasmic reticulum (ER) stress and increasing the ratio of Bax/Bcl-2, leading to the release of cytochrome c and apoptosis-inducing factor

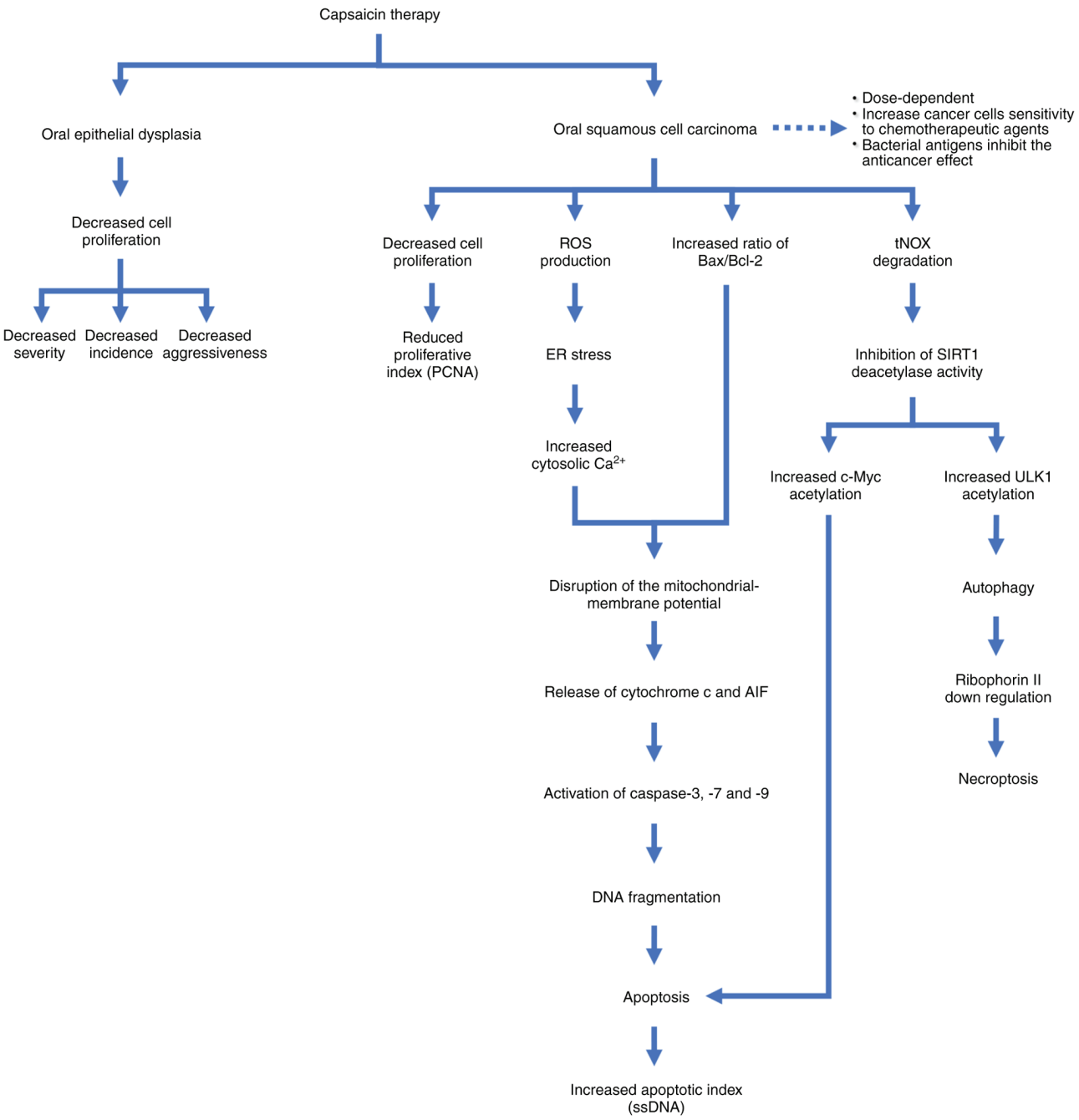

Figure 3. Mechanism of action of capsaicin on oral cancer (54-61). ER, endoplasmic reticulum; ROS, reactive oxygen species; PCNA, proliferating cell nuclear antigen; ssDNA, single-stranded DNA; tNOX, tumor-associated NADH oxidase; SIRT1, sirtuin 1; ULK1, unc-51-like autophagy activating kinase 1.

from mitochondria (56,57). This process activates caspase-3, -7 and -9, resulting in apoptosis (56,57). Furthermore, capsaicin interacts with tumor-associated NADH oxidase (tNOX), promoting both autophagy and apoptosis in cancer cells (59). Capsaicin also enhances the sensitivity of cancer cells to anticancer drugs by increasing autophagy and reducing ribophorin II protein levels (60). However, studies suggest that capsaicin therapy for oral cancer is dose-dependent and its efficacy may be compromised by bacterial antigens (56,61). Considering its multifaceted effects on cellular pathways and its potential implications for developing therapeutic strategies for oral cancer management, further investigations are warranted to truly understand the anti-oral cancer mechanisms of capsaicin.

Oral epithelial dysplasia. Tanaka *et al* (55) found that a 500-ppm capsaicin diet reduced the incidence and multiplicity of tongue dysplasia on 4-NQO-induced tongue tumorigenesis in male rats. In another *in vivo* study, Mohamed and AlQarni (58) experimentally induced hamster buccal pouch carcinogenesis and demonstrated that capsaicin-treated hamsters exhibited slower cell proliferation and reduced incidence and severity of oral epithelial dysplasia.

Oral squamous cell carcinoma. Ip *et al* (56) found that increasing capsaicin doses and longer incubation periods enhanced the induction of apoptosis in NPC-TW 039 cells. Among the doses tested (0, 200, 250, 300 and 400 μM) and

incubation times (12, 24, 36 and 48 h), treatment with 400 μM capsaicin resulted in the most significant decrease in cell viability, reaching nearly 65% after 48 h of treatment (56).

In another *in vitro* investigation focusing on oral squamous cell carcinoma of Asian origin (ORL-48), Kamaruddin *et al* (57) revealed that capsaicin treatment induced apoptosis, leading to apoptotic DNA fragmentation. In addition, the cell viability rate was the lowest, whereas the apoptosis rate was the highest after 72 h of treatment compared with that at 48 h (57).

Chang *et al* (59) investigated the interplay between apoptosis and autophagy in p53-mutated HSC-3 and p53-functional SAS cells treated with different concentrations of capsaicin. They revealed that capsaicin engaged with tumor-associated NADH oxidase (tNOX) to cause its degradation, and inhibition of sirtuin 1 (SIRT1) deacetylase activity, which enhanced unc-51-like autophagy activating kinase 1 (ULK1) acetylation and autophagy activation in p53-functional SAS cells (59). Capsaicin induced autophagy and apoptosis in p53-mutated HSC-3 cells, with autophagy inhibiting but later facilitating apoptosis. Reduced tNOX and SIRT1 levels, combined with high levels of ULK1 and c-Myc acetylation, reactivated the tumor necrosis factor-related apoptosis-inducing ligand pathway, resulting in apoptosis (59).

Huang *et al* (60) investigated capsaicin-induced sensitization to four chemotherapeutic agents (5-fluorouracil, cisplatin, docetaxel and doxorubicin) in oral squamous cell carcinoma (HSC-3 and SAS) and discovered that 200 μM capsaicin did not significantly induce apoptosis but caused ER stress and autophagy by suppressing ribophorin II. Furthermore, capsaicin in combination with anticancer agents sensitizes cancer cells to these agents and inhibits their viability by increasing necroptosis markers such as mixed lineage kinase domain-like protein and receptor-interacting protein kinase 3 (60).

5. Antimicrobial properties

The chili fruit is rich in phenolic compounds, predominantly flavonoids and capsaicin, alongside phenolic acids such as tamarind ferulic, coumaric acid and cinnamic acid (62,63). These secondary metabolites are positively associated with antioxidant and antimicrobial activities, potentially interfering with the synthesis of bacterial cell membranes (64). Numerous studies have proved the antimicrobial properties of capsaicin, providing a promising standpoint as an alternative strategy against antimicrobial resistance (65).

Dental caries. Santos *et al* (66) evaluated the inhibitory effects of capsaicin, dihydrocapsaicin and four synthetic capsaicinoid derivatives against *Streptococcus mutans*, a key contributor to cariogenic biofilm. They revealed that these compounds had a minimum inhibitory concentration (MIC) ranging from 1.25 to 5.0 μg/ml for these bacteria (66). Similarly, Gu *et al* (67) demonstrated the potent action of capsaicin against cariogenic bacterial strains, including *S. mutans*, *Actinomyces viscosus*, *Lactobacillus* and *Streptococcus sanguis*, by inhibiting acid production and biofilm formation. The MIC values of capsaicin were 50 μg/ml for *S. mutans*, *A. viscosus* and *Lactobacillus* and 25 μg/ml for *S. sanguis* (67). However, Doğan and Tunçer (68) reported contrasting findings: Although capsaicin did not inhibit the growth of *S. mutans*, it suppressed the growth of the oral probiotic *Streptococcus salivarius* M18 at concentrations >100 μg/ml. These discrepancies underscore the need for further studies into the nuanced effects of capsaicin, considering factors such as compound nature and concentration, and its effect on nonpathogenic oral bacteria.

Periodontal diseases. Previous studies have also highlighted the efficacy of capsaicin against periodontitis-associated pathogens, notably *P. gingivalis*. An *in vitro* study by Zhou *et al* (13) demonstrated the inhibitory effect of capsaicin on the growth of *P. gingivalis* and the expression of NF-κB p65, indicating its potential to inhibit alveolar bone resorption. In addition, animal experimental studies, such as that by Cong *et al* (69), revealed that topical application of 0.075% capsaicin over the submandibular gland increased salivary secretion, which could have a significant utility in the control of microbial colonization.

Candidiasis. Investigations into the antifungal properties of capsaicin, particularly against *Candida albicans*, a common cause of oral candidiasis infections, have yielded promising results (65). Nascimento *et al* (70) found that at the MIC of 25 μg/ml, capsaicin inhibited the growth of *C. albicans*. Furthermore, Omolo *et al* (71) highlighted greater susceptibility of *C. albicans* to capsaicin than certain bacterial strains. Behbehani *et al* (72) proposed the mechanism of capsaicin's antifungal activity, suggesting its ability to disrupt *C. albicans* cell wall integrity by inhibiting ergosterol biosynthesis. In addition, the combination of capsaicin and fluconazole exhibited enhanced efficacy, potentially aiding in preventing fluconazole resistance (72).

Viral infection of the oral cavity. Despite studies investigating the potential antiviral properties of capsaicin, particularly against Herpes simplex virus (73), Lassa virus (74,75) and severe acute respiratory syndrome coronavirus 2 (75), research on its effects on oral viruses is limited. Nevertheless, considering capsaicin's potential to inhibit the replication of certain viruses because of its ability to modulate immune and inflammatory responses (76), further related research could provide valuable insight into its therapeutic potential for viral infections in the oral cavity.

6. Side effects

Mild to moderate burning sensation, stinging, itching, redness and pain in the treated area are among the main reported side effects of topical treatment of capsaicin for orofacial pain and disorders, which are self-limiting and short term (37-39,43). Studies have recommended administering a local anesthetic before applying topical capsaicin to minimize pain perception and control the initial burning sensation (32,35). Ensuring the patch fits the contour of the affected skin and avoiding contact with the eyes are also essential for the treatment's safety (38).

However, topical therapy requires repeated applications daily, which could expose patients to repeated potential irritations from side effects, reducing the patient's compliance with the therapy (31,36). Furthermore, capsaicin's bitter taste and unpleasant consistency contributed to lower compliance with the therapy, particularly when applied on the tongue (42).

In addition, further research on the intraoral use of capsaicin is warranted to investigate potential side effects on the gastrointestinal system. Petruzzi *et al* (42) reported mild gastric pain in patients treated with oral systemic capsaicin for BMS symptoms. Jørgensen and Pedersen (44) reported that several patients discontinued the capsaicin gel therapy that required application on the tongue for treating BMS because of nausea and sore throat.

7. Conclusion and future perspectives

Capsaicin holds significant promise for enhancing oral health owing to its analgesic, anti-inflammatory, anticancer and antimicrobial effects. However, more studies are necessary to determine the optimal dosage of capsaicin for alleviating oral pain while minimizing adverse effects. Further investigations on the effect of capsaicin on nonpathogenic oral bacteria and oral viruses are also warranted. Human-based research is also needed to gain a deeper understanding of the biomolecular mechanisms underlying the properties of capsaicin. These research advancements could lead to the development of more effective and targeted interventions for oral health issues.

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Authors' contributions

The study was conceptualized by WY. WY and AR significantly contributed to data collection, manuscript drafting, reviewing and editing. Each author has thoroughly reviewed and approved the final version of the manuscript. Data authentication is not applicable.

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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