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Exploring Capsaicin-Based Drug Delivery Systems for Cancer Treatment: A Review

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Abstract

There have been studies on the possible use of capsaicin as a treatment for cancer, and some of these studies have explored the use of capsaicin-based drug delivery systems. Nanocarrier-based drug delivery systems have been designed for the release of capsaicin for the prevention and treatment of cancer. Recent advances have been made in the field of nanomedicine and nanotechnology, which have the potential to aid in the treatment of various diseases. The use of capsaicin in conjunction with traditional chemotherapy agents or radiation treatment has been explored as a promising strategy for cancer treatment. Some studies have found that sustained release drug delivery systems based on capsaicin have shown efficacy in cancer chemotherapy. However, additional study is required to fully understand the potential of capsaicin-based delivery systems for cancer treatment.

***Keywords*:** Capsaicin; Drug delivery; Cancer; Apoptosis; Metastasis

1. Introduction

Capsaicinoids are a class of chemicals that give fiery chile peppers (Capsicum annuum and Capsicum frutescens) their spicy, pungent flavor [1, 2]. Capsaicin, nonivamide, homohydrocapsaicin, dihydrocapsaicin, homodihydrocapsaicin, and nondihydrocapsaicin are the most common capsaicinoids. Capsaicin's "heat sensation" is caused by its attachment to ion channel receptors for transient receptor potential vanilloid (TRPV) [3]. Capsaicin is a TRPV1 receptor agonist with strong sensitivity [4]. Other capsaicinoids besides capsaicin cause the "heat sensation" via the TRPV1 receptor. The pharmacological action of capsaicin like substances is affected by a number of variables, including the dosage, method of administration, and, most significantly, focusing on target tissues. Capsaicinoids, and particularly capsaicin, have been shown to have a wide range of biological and physiological activities, including antioxidants [5], anticarcinogenics [6], energy metabolism promotion and fat accumulation suppression [7], and anti-inflammatories [8]. However, the irritation produced by these molecules pungency limits their potential uses. Capsaicin is well known for its tumor prevention and antitumor properties. However, because of its hydrophobicity, poor affinity, and brief half-life, capsaicin's clinical application is severely restricted. Nanoparticles (NPs) have sparked considerable interest in recent years owing to their capability to improve the possible therapeutic value of different agents while reducing associated adverse effects. Currently, a wide range of nanoparticles, including gadolinium, gold, hafnium, ferromagnetic, silicon, and polymer nanoparticles, nanorods, nanotubes, liposomes, quantum dots, and dendrimers, have been studied and used in drug delivery systems in experimental or clinical settings [9, 10].

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2. Capsaicin's mechanism of action

Capsaicin binds to transient receptor potential vanilloid 1 (TRPV1), also named the vanilloid receptor, and is found primarily in sense neurons [11]. TRPV1 was discovered and cloned in rats and includes 838 amino acids and a molecular weight of 95 kDa in both rats and humans, with six transmembrane domains and a developing short pore area between the fifth and sixth transmembrane domains [12]. This is a nonselective receptor, ligand operated cationic channel found mainly in nociceptive neurons small filaments. TRPV1 is also found in the bladder, kidneys, bowels, brain, epidermal keratinocytes, glial cells, polymorphonuclear granulocytes, liver, macrophages, and mast cells [11, 13]. It can be present in the plasma membrane as well as the endoplasmic reticulum, where it pairs with a nonspecific cation channel receptive to sodium and calcium ions and controls intracellular calcium levels [14, 15]. This channel can be regulated and activated by endogenous substances such as endovanilloids as well as a variety of exogenous stimuli such as chemical agonists such as olvanil, capsaicin, and resiniferatoxin, which are highly lipophilic ligands with structural similarities to several endogenous amounts of topical capsaicin result in temporary sensitivity but no long-term effects. High amounts can induce nerve fiber degeneration [20], as well as a temporary decrease in the number of epidermal nerve fibers [21]. This is thought to underpin the analgesic fatty acids referred to as TRPV1 agonists [16]. Capsazepine, iodoresiniferatoxin, ruthenium red, A-425619, AMG9810, SB-366791, and SB-705498 are among the substances used as TRPV1 inhibitors [17]. A heat-sensitive component of TRPV1 is responsible for the burning sensation produced by capsaicin. Capsaicin binding to TRPV1 raises intracellular calcium, causing the production of substances P and the calcium gene-related peptide are examples of neuropeptides (CGRP). When capsaicin comes into contact with sensory nerves, it causes discomfort, inflammation, and a concentrated burning feeling. When administered directly to the epidermis, it supports analgesia by desensitizing sensory neurons induced by substance P depletion [18].

3. Capsaicin's pharmacodynamic effect

An alkylamide called capsaicin was discovered in capsicum chili pepper plants. The burning and heat feelings caused by capsaicin touch and ingestion are caused by the stimulation of an ion channel named transient receptor potential vanilloid 1 (TRPV1) Fig. 1, which is produced by nociceptive afferent neurons. Channels are opened, enabling Ca^{++} and Na^{+} to enter and cause cell excitation. Capsaicin causes channel desensitization, which results in the analgesic curative action linked with capsaicin [19]. Low effects of large amounts of topical capsaicin and is being investigated as a potential long-term permanent pain reduction pathway [22].

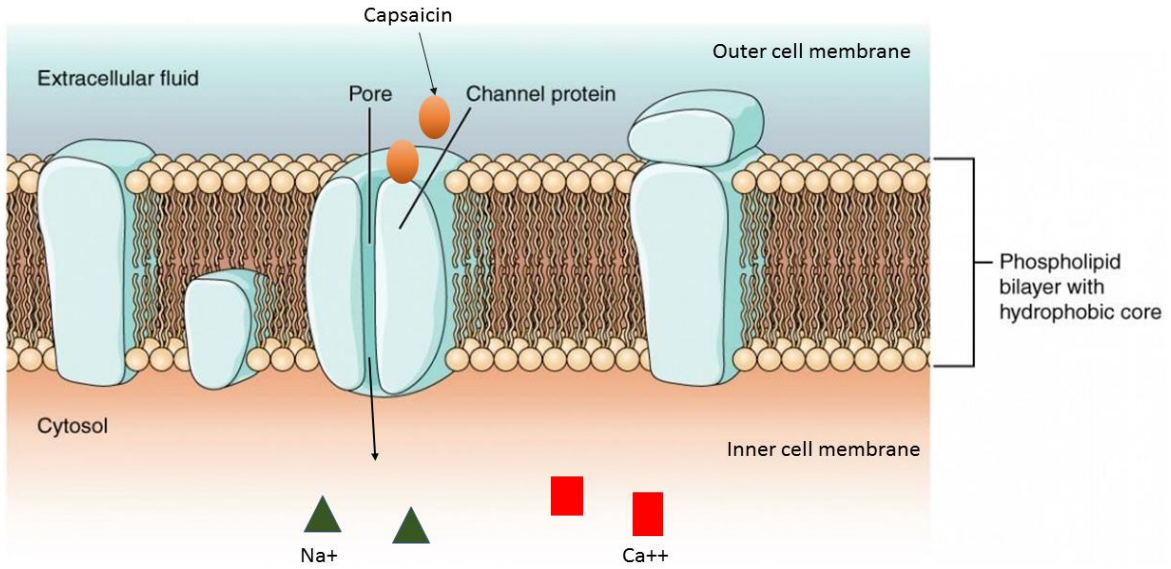

Fig. 1 Pharmacodynamics action of capsaicin

4. Capsaicin chemoprevention

Cancer therapy is presently a hot subject because of how serious it is, effect about life quality, and financial the healthcare system's burden. Despite advances in the science of medicine, the cancer load continues to rise quickly, necessitating the development of safer and more efficient cancer prevention and therapy methods adequate for inhibiting or curing cancer [23]. Most current treatment methods have failed due to the fact that various types of cancer can acquire mutations that make them immune to therapy over time. Chemoprevention is the use of chemotherapeutic drugs to slow or stop tumor growth before tumor cell invasion occurs [24]. As described further below, capsaicin has shown considerable promise as an efficient chemopreventive agent.

5. Capsaicin anti-mutagenic

The first proof of capsaicin's anticancer function could be linked back to earlier research on chemopreventive and anti-carcinogenic action. Capsaicin pretreatment inhibited lung cancer in a rodent model by suppressing benzo's DNA binding (a) pyrene (a polycyclic aromatic hydrocarbon carcinogen) [25]. Several investigations have found capsaicin to be safe in opposition to carcinogens found in chemicals such as aflatoxin B1, vinyl carbamate, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and N-nitrosodimethylamine [26]. It is worth noting that many of these hydrocarbons (particularly halogenated hydrocarbons) are processed by the phase enzyme that metabolizes drugs, CYP450 2E1, which induces activation to produce highly reactive genotoxic products. It has been proven that capsaicin blocks several CYP 450 enzyme variants, including CYP 2E1. As a result, the capacity of capsaicin to modulate CYP enzymes has been connected to its chemoprotective function. Furthermore, in recent research, capsaicin was shown to activate Ca^{2+}/calmodulin (CaM)-dependent protein kinase (CaMK) and CCAAT/enhancer-binding protein (C/EBP), resulting in the simultaneous suppression of CYP1A1 mRNA [27]. Capsaicin can thus function as an anti-carcinogenic drug by suppressing the expression of CYP enzymes and their upstream modulators.

6. Capsaicin anti-oxidative action

Capsaicin directly scavenges free radicals while also increasing the production of several antioxidant enzymes. There was a favorable relationship between capsaicin and its derivatives and the activity of antioxidants of capsicum chilies [28]. Capsaicin has also been shown to shield linoleic acid from autoxidation and Fe^{2+} induced oxidation [29]. Furthermore, capsaicin suppresses oxidized low density lipoprotein induced reactive oxygen species (ROS) release and consequent mitochondrial membrane potential collapse, chromosome condensation, cytochrome c expression, and caspase-3 activation in human umbilical vein endothelial cells [30]. This significant activity of free radical scavenging lends credibility to the compound's ability to mitigate oxidative stress conditions, which have been linked to cellular dysfunction and the formation of cancer. Furthermore, capsaicin synergistically work with other dietary phytochemicals, resulting in an exponentially advantageous cytoprotective impact [31, 32]. Joung et al. [33] research offered additional molecular insights into capsaicin's antioxidant defense mechanism. The scientists discovered that capsaicin could activate the HepG2 cells antioxidant defense response by promoting a sequence of protein kinase phosphorylation events. Capsaicin has been shown to phosphorylate Akt, triggering the protein kinase and resulting in Nrf2 activation. Phosphorylation of Nrf2 disrupts the NRF2/Keap 1 complex, allowing the Nrf2 protein that has been activated to translocate to the nucleus and form a compound with Maf2, which interacts with the antioxidant response element in the promoter region of genes producing heme-oxygenase-1, an antioxidant enzyme. HO-1 catalyzes the oxidative breakdown of heme to produce liberated carbon monoxide, heme, and biliverdin. HO-1 protects against heme protein oxidative injury by decomposing heme. Aside from HO-1, Nrf2 stimulation has been related to higher expression of other and NAD(P)H-metabolizing enzymes: quinone acceptor oxidoreductase (NQO) and antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione s- transferase (GST), and glutathione peroxidase (GPx) via the Nrf2/ARE pathway as shown in **Fig. 2**.

7. Capsaicin anti-inflammatory action

Inflammation that lasts a long time has been identified as a significant risk factor for cancer. This is due to persistent inflammation causes significant harm to the structure of DNA, which can lead to cancer. This is seen in persistent inflammatory bowel

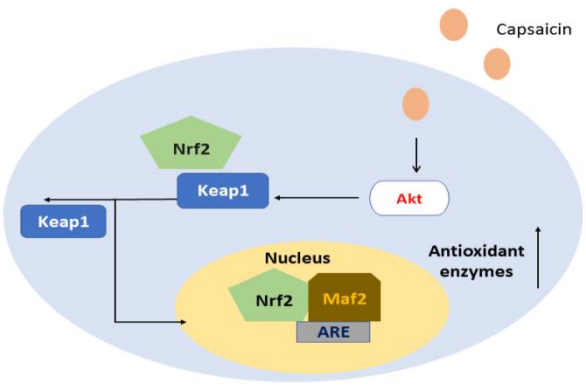

Fig. 2 Nrf2/ARE pathway of capsaicin antioxidative action

diseases like ulcerative colitis and Crohn's disease, which contribute to colon cancer. Capsaicin sub-plantar injections substantially reduced wistar rat paw swelling at a pace similar to the usual drug diclofenac [34]. Capsaicin's anti-inflammatory impact was first connected to capsaicin receptors known as transient receptor potential vanilloid sub-type1. Tissue injury has been related to vanilloid receptors and inflammation. However, capsaicin causes anti-inflammatory reactions via these receptors when applied repeatedly. According to recent research, capsaicin's anti-inflammatory effect is autonomous of the TRPV1 receptor. [35–37]. Capsaicin inhibits lipopolysaccharide (LPS)-induced IL-1, IL-6, and TNF-production by boosting Liver X receptor (LXR) expression via the peroxisome proliferator-activated receptor-gamma (PPAR) pathway [35]. The authors also discovered that LXR activation inhibits NF-B-mediated inflammatory gene expression, and that LXR silencing with siRNA inhibits capsaicin's inhibitory effect on NF-B expression. Similarly, capsaicin suppresses the production of pro-inflammatory cytokines by toll-like receptor-mediated salivary epithelial cells via the NF-kB signaling pathway. Capsaicin inhibits NF-kB via a process involving ikB- breakdown, according to Kim et al. [36]. To reduce inflammation in LPS-stimulated mouse peritoneal macrophages, the substance inhibits COX-2 enzyme activity and downregulates the iNOS protein. Chen et al. [38] examined the signal transduction pathway involved in capsaicin's anti-inflammation activity in RAW264.7 macrophages. Capsaicin suppressed nitric oxide (NO) synthesis mediated by LPS and IFN, as well as iNOS protein and mRNA expression, COX-2 expression, and PGE2 generation. Furthermore, capsaicin suppresses the stimulation of NF-B, AP-1, and STAT1, as well as other upstream protein kinases such as ERK, JNK, and IKK. Capsaicin's apoptotic activity is linked to the suppression of the upstream enzyme.

8. Capsaicin and cell cycle control

During cell proliferation, a cell goes through the G0/G1, S, and G2/M stages of the cell cycle. The cyclin dependent kinase, cyclin, and checkpoint kinases, such as aurora kinase, polo-like kinase, and CDK inhibitors, tightly control this chain of events to prevent damaged or mutant cells from continuing through the cell cycle. Cell cycle control is aberrant in cancer cells, which permits cell growth. Over time, dietary phytochemicals like capsaicin have demonstrated appealing cell cycle control action, stopping the proliferation of cancer cells at the cellular level [39]. A cell enters the growth phase after becoming sensitized by a proliferative stimulation and leaving the resting G0 phase. In ORL-48 cells, a recent research found that capsaicin promotes cell cycle arrest at the G1 phase [40]. Similarly, Qian et al. [41] bladder cancer cells treated with capsaicin have been found to experience G0/G1 cell cycle arrest. However, research has also shown that human KB cancer cells and MCF7 breast cancer cells exhibit G2/M cell cycle suppression. Cell cycle protein kinases are often modulated in order to cause cellular arrest. For instance, capsaicin caused the G2/M phase arrest of breast cancer cells by downregulating CDK8 expression [42]. In another research, G0/G1 arrest was caused by CDK2 inhibition, CDK4 inhibition, and CDK6 inhibition [43]. Likewise, the anti-tumor impact of capsaicin in human pharyngeal squamous carcinoma cells (FaDu) is linked to mitochondrial pathways, potentially through lowering the expression of cyclin B1 and D1 regulators, as well as cyclin-dependent protein kinases CDK-1, CDK-2, and CDK-4, which mediate cell cycle arrest at G1/S phase [44]. Capsaicin regulates upstream molecular processes such as the p53 dependent pathways in addition to its anti-CDK action. Islam et al. [45] It was recently discovered that tumor-associated NADH oxidase (tNOX) is a primary target of capsaicin that is responsible for its cell cycle action. The scientists observed that regulating tNOX lowers NAD+ synthesis and inhibits SIRT1, resulting in c-myc and p53 activation and, eventually, suppression of the cyclin/CDK complex at the G1 checkpoint, resulting in cell cycle arrest. Capsaicin therapy in bladder cancer reduces tNOX and SIRT1 expression, hence extending cell cycle progression, among other effects [46]. In human colon cancer cells, capsaicin induces an anticancer effect via a p53-dependent mechanism. Capsaicin reduced p53 degradation by decreasing the p53/MDM2 interaction, allowing p53 to trigger cell cycle arrest during the G0/G1 phase and death [47]. Furthermore, capsaicin modifies the expression of CDK2, p53, and p21, beginning G0/G1 phase arrest in bladder cancer RT4 cells by a mechanism involving the vanilloid receptor TRPV1 [48]. Overall, by altering important cell cycle signal transducers, capsaicin inhibits cancer development by halting cancer growth in several cancer types.

9. Capsaicin's apoptotic cell death mechanism

The main method by which capsaicin induces cell death in cancer cells is apoptosis. Apoptosis is a type of planned cell death marked by physical and molecular processes such as cell shrinkage, nuclear membrane blebbing, DNA fragmentation, chromatin condensation, and engulfment of deceased cells by neighboring cells [49]. Following capsaicin therapy of cancer cells, a new molecular pathway capable of causing apoptosis has been characterized. Vanilloid receptors are one of capsaicin's key pro-apoptotic pathways, specifically TRPV1, a nonselective

calcium channel that has been implicated in cell death in a broad range of tumor cells. Capsaicin treatment boosted TRPV1 mRNA in glioma cells, resulting in a Ca^{2+} influx that triggered death through the p38 signaling pathway [50]. As well, in anaplastic thyroid cancer, capsaicin's agonistic function resulted in viability of cells inhibition as a consequence of cell death through the intrinsic apoptosis pathway. Ca^{2+} influx into the cell cytoplasm was also triggered, resulting in a mismatch in intracellular calcium equilibrium and a serious state of mitochondrial overload of calcium [51]. The disturbance of the mitochondrial calcium balance led to an increase in the generation of reactive oxygen species in the mitochondria, depolarization of the mitochondrial membrane potential, and the opening of the mitochondrial membrane permeability pore. The latter has an impact results in the release of cytochrome C, which causes apoptosis and caspase stimulation, resulting in apoptotic cell death. The research also demonstrated that in the presence of a TRPV1 antagonist and calcium chelator, apoptosis develops, highlighting the involvement of the TRPV1 receptor pathway in capsaicin caused tumor cells to die [51].

10. Capsaicin and cancer metastasis

Tumor cells can migrate through blood systems or the lymphatic to invade remote locations in some instances, a process known as metastasis. Capsaicin has previously been shown to reduce the metastasis of cancer due to its ability to regulate key pathways taking part in cancer molecular changes. The creation of newly formed blood vessels to transport oxygen and nutrients required for secondary tumor growth is known as angiogenesis. Capsaicin can slow the development of secondary tumors by blocking angiogenesis. Capsaicin inhibited angiogenesis in non-small lung cancer cells by suppressing vascular endothelial growth factor (VEGF) production via the p53-SMAR1 auto-regulatory loop [52]. Capsaicin can also prevent tumor spread by blocking the matrix proteolysis pathway. Capsaicin has been demonstrated to specifically target matrix metalloproteinase 9 (MMP9), a protein involved in the degradation of extracellular matrix and cytokine capsaicin delivery systems with enhanced pharmacokinetic characteristics have been developed [60]. **Table 1** highlights research on the stimulation during metastatic cancer tissue remodeling. Capsaicin inhibits MMP9 by suppressing the AMPK-NF-B, EGFR-mediated PKC/Raf/ERK, FAK/Akt, p38 MAPK, and AP-1 signaling pathways [53, 54]. Inhibition of the phosphatidylinositol 3-kinase/Akt/Rac1 signal pathway is the main cause of cell migration in B16-F10 melanoma. Capsaicin suppresses matrix proteases MMP9 and MMP2 in human papillary thyroid carcinoma BCPAP cells by triggering the TRPV1 channel. [55]. According to new findings [56], capsaicin may suppress esophageal squamous cell carcinoma (ESCC) migration, invasion, and metastasis by overexpressing claudin-3 (Cldn3) and blocking epithelial-mesenchymal transition (EMT). Capsaicin's anti-metastatic impact was further confirmed in an in vivo mouse prostate cancer model, where it was shown that capsaicin greatly decreased the metastatic burden [57].

11. Nanotechnology

Nanoparticles that have been engineered are used to cure illnesses in nanomedicine, a biomedical application of nanotechnology. Because of its novel imaging and therapeutic powers, nanomedicine has the potential for early cancer detection and therapy. Nanoparticle-based cancer therapies provide a new way of delivering anticancer medications directly to tumor cells and drug resistant cancer cells in sufficient amounts, resulting in increased target cell accumulation and fewer adverse effects associated with high dose chemotherapy [58, 59].

12. Capsaicin-nanocarriers delivery system

To improve bioavailability, pharmacokinetics, and half-life, as well as to reduce side effects, various delivery vehicles, including inorganic carriers (carbon spheres and metal nanoparticles), polymeric carriers (dendrimer, micelle, and polymersome), and lipid-based nanoparticles (microencapsulation, liposomes, and solid-lipid nanoparticle), have been created. Furthermore, excipient-free, self-assembled

administration of capsaicin for increased anticancer effects.

Table 1 Clinical trials of capsaicin loading on nanocarriers for delivery

Delivery system	Cancer type	Conclusion	Reference
Capsaicin is nano-encapsulated on a lipid vesicle.	Hepatocellular carcinoma	Has therapeutic promise in lowering hepatic oxidative stress brought on by several stressors	[61]
Lipid nanoparticles with folic acid linked to capsaicin	Ovarian cancer	Enhance capsaicin's ability to actively target ovarian tumors	[62]
Trimethylchitosan-based nanoparticles loaded with capsaicin	Hepatocellular carcinoma	Anti-cancer drug that effectively caused human HepG2 hepatocarcinoma cells to undergo apoptosis. Additionally, the MDR-1 gene's potential contribution to enhancing chemotherapy response has been seen through its downregulation	[63]
Capsaicin loaded albumin nanoparticles	Inflammation/ cancer	The albumin nanoparticles are prospective capsaicin carriers useful in a variety of illnesses, such as inflammation and cancer	[64]
Capsaicin loaded hyaluronic acid nanoparticles	Lung cance	The drug delivery device demonstrated significant anticancer effect *in vitro* and *in vivo*	[65]
Capsaicin-BODIPY selfassembly	Prostate cancer	Nanosystem demonstrated tremendous biological promise and guaranteed an active cancer target	[66]
Inclusion complexes of capsaicin in cyclodextrin put into pegylated liposomes	Breast cancer cells	Capsaicin administration through liposomes enhanced chemopreventive function	[67]

13. Conclusions

In conclusion, capsaicin-based delivery systems have shown potential for cancer treatment, as demonstrated by various studies exploring the use of sustained-release drug delivery systems and combination with conventional chemotherapy drugs or radiotherapy. Nanocarrier-based drug delivery systems have also been developed for the release of capsaicin for the prevention and treatment of cancer. However, more study is needed to fully understand the efficacy and potential of capsaicin-based delivery systems for cancer treatment. Further studies should be conducted to investigate the optimal dosage, administration frequency, and potential side effects of capsaicin based delivery systems for cancer treatment.

14. List of abbreviations

TRPV	Transient receptor potential vanilloid
NPs	Nanoparticles
CGRP	Calcium gene-related peptide
CaM	Ca^{2+}/calmodulin
CaMK	Ca^{2+}/calmodulin (CaM)-dependent protein kinase
C/EBP	CCAAT/enhancer-binding protein
ROS	Reactive oxygen species
NQO	Quinone acceptor oxidoreductase
CAT	Catalase
LPS	Lipopolysaccharide
LXR	Liver X receptor
PPAR	Peroxisome proliferator-activated receptor
tNOX	Tumor-associated NADH oxidase
VEGF	Vascular endothelial growth factor
MMP9	Matrix metalloproteinase 9
ESCC	Esophageal squamous cell carcinoma
Cldn3	Claudin-3
EMT	Epithelial-mesenchymal transition
SOD	Superoxide dismutase
GST	Glutathione s- transferase
GPx	Glutathione peroxidase
NO	Nitric oxide
FaDu	Pharygeal squamous carcinoma cells

15. Conflicts of interest

There are no conflicts to declare.

16. Formatting of funding sources

No funds, grants, or other support was received.

17. References

1. Reyes-Escogido, M. de L., Gonzalez-Mondragon, E. G., & Vazquez-Tzompantzi, E. (2011). Chemical and Pharmacological Aspects of Capsaicin. Molecules, 16(2), 1253–1270. https://doi.org/10.3390/molecules16021253

2. Vs, G., & Mn, S. (1991). Capsicum--production, technology, chemistry, and quality. Part V. Impact on physiology, pharmacology, nutrition, and metabolism; structure, pungency, pain, and desensitization sequences. Critical reviews in food science and nutrition, 29(6). https://doi.org/10.1080/10408399109527536

3. Caterina, M. J., & Julius, D. (2001). The vanilloid receptor: a molecular gateway to the pain pathway. Annual Review of Neuroscience, 24, 487–517. https://doi.org/10.1146/annurev.neuro.24.1.487

4. J, O., C, B., Ae, O., T, A., M, N., & Ah, D. (2012). Unravelling the mystery of capsaicin: a tool to understand and treat pain. Pharmacological reviews, 64(4). https://doi.org/10.1124/pr.112.006163

5. Luo, X.-J., Peng, J., & Li, Y.-J. (2011). Recent advances in the study on capsaicinoids and capsinoids. European Journal of Pharmacology, 650(1), 1–7. https://doi.org/10.1016/j.ejphar.2010.09.074

6. Sharma, S. K., Vij, A. S., & Sharma, M. (2013). Mechanisms and clinical uses of capsaicin. European Journal of Pharmacology, 720(1–3), 55–62. https://doi.org/10.1016/j.ejphar.2013.10.053

7. Remadevi, R., & Szallisi, A. (2008). Adlea (ALGRX-4975), an injectable capsaicin (TRPV1 receptor agonist) formulation for longlasting pain relief. IDrugs: the investigational drugs journal, 11(2), 120–132.

8. Wong, G. Y., & Gavva, N. R. (2009). Therapeutic potential of vanilloid receptor TRPV1 agonists and antagonists as analgesics: Recent advances and setbacks. Brain Research Reviews, 60(1), 267–277. https://doi.org/10.1016/j.brainresrev.2008.12.006

9. Zhang, W., Liu, M., Liu, A., & Zhai, G. (2017). Advances in Functionalized Mesoporous Silica Nanoparticles for Tumor Targeted Drug Delivery and Theranostics. Current Pharmaceutical Design, 23(23), 3367–3382. https://doi.org/10.2174/1381612822666161025153619

10. Spyratou, E., Makropoulou, M., Efstathopoulos, E. P., Georgakilas, A. G., & Sihver, L. (2017). Recent Advances in Cancer Therapy Based on Dual Mode Gold Nanoparticles. Cancers, 9(12), 173. https://doi.org/10.3390/cancers9120173

11. Cortright, D. N., & Szallasi, A. (2004). Biochemical pharmacology of the vanilloid receptor TRPV1. European Journal of Biochemistry, 271(10), 1814–1819. https://doi.org/10.1111/j.1432-1033.2004.04082.x

12. Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D., & Julius, D. (1997). The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature, 389(6653), 816–824. https://doi.org/10.1038/39807

13. Tominaga, M., & Tominaga, T. (2005). Structure and function of TRPV1. Pflügers Archiv, 451(1), 143–150. https://doi.org/10.1007/s00424-005-1457-8

14. Kárai, L. J., Russell, J. T., Iadarola, M. J., & Oláh, Z. (2004). Vanilloid Receptor 1 Regulates Multiple Calcium Compartments and Contributes to Ca2+-induced Ca2+ Release in Sensory Neurons *. Journal of Biological Chemistry, 279(16), 16377–16387. https://doi.org/10.1074/jbc.M310891200

15. Liu, M., Liu, M.-C., Magoulas, C., Priestley, J. V., & Willmott, N. J. (2003). Versatile Regulation of Cytosolic Ca2+ by Vanilloid Receptor I in Rat Dorsal Root Ganglion Neurons *. Journal of Biological Chemistry, 278(7), 5462–5472. https://doi.org/10.1074/jbc.M209111200

16. Morita, A., Iwasaki, Y., Kobata, K., Iida, T., Higashi, T., Oda, K., … Watanabe, T. (2006). Lipophilicity of capsaicinoids and capsinoids influences the multiple activation process of rat TRPV1. Life Sciences, 79(24), 2303–2310. https://doi.org/10.1016/j.lfs.2006.07.024

17. Pingle, S. C., Matta, J. A., & Ahern, G. P. (2007). Capsaicin Receptor: TRPV1 A Promiscuous TRP Channel. In V. Flockerzi & B. Nilius (Eds.), Transient Receptor Potential (TRP) Channels (pp. 155–171). Berlin, Heidelberg: Springer. https://doi.org/10.1007/978-3-540-34891-7_9

18. Bevan, S., & Szolcsányi, J. (1990). Sensory neuron-specific actions of capsaicin: mechanisms and applications. Trends in Pharmacological Sciences, 11(8), 331–333. https://doi.org/10.1016/0165-6147(90)90237-3

19. Curry, J., Aluru, M., Mendoza, M., Nevarez, J., Melendrez, M., & O'Connell, M. A. (1999). Transcripts for possible capsaicinoid biosynthetic genes are differentially accumulated in pungent and non-pungent Capsicum spp. Plant Science, 148(1), 47–57. https://doi.org/10.1016/S0168-9452(99)00118-1

20. Aluru, M. R., Mazourek, M., Landry, L. G., Curry, J., Jahn, M., & O'Connell, M. A. (2003). Differential expression of fatty acid synthase genes, Acl, Fat and Kas, in Capsicum fruit. Journal of Experimental Botany, 54(388), 1655–1664. https://doi.org/10.1093/jxb/erg176

21. Andrews, J. (1995). Peppers: The Domesticated Capsicums. University of Texas Press.

22. Stewart Jr, C., Kang, B.-C., Liu, K., Mazourek, M., Moore, S. L., Yoo, E. Y., … Jahn, M. M. (2005). The Pun1 gene for pungency in pepper encodes a putative acyltransferase. The Plant Journal, 42(5), 675–688. https://doi.org/10.1111/j.1365-313X.2005.02410.x

23. Zhang, Q., Hou, D., Wen, X., Xin, M., Li, Z., Wu, L., & Pathak, J. L. (2022). Gold nanomaterials for oral cancer diagnosis and therapy: Advances, challenges, and prospects. Materials Today Bio, 15, 100333. https://doi.org/10.1016/j.mtbio.2022.100333

24. Elekofehinti, O. O., Iwaloye, O., Olawale, F., & Ariyo, E. O. (2021). Saponins in Cancer Treatment: Current Progress and Future Prospects. Pathophysiology: The Official Journal of the International Society for Pathophysiology, 28(2), 250–272. https://doi.org/10.3390/pathophysiology28020017

25. Anandakumar, P., Kamaraj, S., Jagan, S., Ramakrishnan, G., Asokkumar, S., Naveenkumar, C., … Devaki, T. (2012). Capsaicin inhibits benzo(a)pyrene-induced lung carcinogenesis in an in vivo mouse model. Inflammation Research, 61(11), 1169–1175. https://doi.org/10.1007/s00011-012-0511-1

26. Ahmad, A., Sakr, W. A., & Rahman, K. M. W. (2010). Anticancer properties of indole compounds: mechanism of apoptosis induction and role in chemotherapy. Current Drug Targets, 11(6), 652–666. https://doi.org/10.2174/138945010791170923

27. Han, E. H., Hwang, Y. P., Kim, H. G., Choi, J. H., Park, B. H., Song, G. Y., … Jeong, H. G. (2011). CCAAT/ enhancer-binding protein β activation by capsaicin contributes to the regulation of CYP1A1 expression, mediated by the aryl hydrocarbon receptor. British Journal of Pharmacology, 164(6), 1600–1613. https://doi.org/10.1111/j.1476-5381.2011.01232.x

28. Sora, G. T. S., Haminiuk, C. W. I., da Silva, M. V., Zielinski, A. A. F., Gonçalves, G. A., Bracht, A., & Peralta, R. M. (2015). A comparative study of the capsaicinoid and phenolic contents and in vitro antioxidant activities of the peppers of the genus Capsicum: an application of chemometrics. Journal of Food Science and Technology, 52(12), 8086–8094. https://doi.org/10.1007/s13197-015-1935-8

29. Rosa, A., Deiana, M., Casu, V., Paccagnini, S., Appendino, G., Ballero, M., & Dessí, M. A. (2002). Antioxidant activity of capsinoids. Journal of Agricultural and Food Chemistry, 50(25), 7396–7401. https://doi.org/10.1021/jf020431w

30. Chen, K.-S., Chen, P.-N., Hsieh, Y.-S., Lin, C.-Y., Lee, Y.-H., & Chu, S.-C. (2015). Capsaicin protects endothelial cells and macrophage against oxidized low-density lipoprotein-induced injury by direct antioxidant action. Chemico-Biological Interactions, 228, 35–45. https://doi.org/10.1016/j.cbi.2015.01.007

31. Tanrıkulu-Küçük, S., Başaran-Küçükgergin, C., Seyithanoğlu, M., Doğru-Abbasoğlu, S., Koçak, H., Beyhan-Özdaş, Ş., & Öner-İyidoğan, Y. (2019). Effect of dietary curcumin and capsaicin on testicular and hepatic oxidant-antioxidant status in rats fed a high-fat diet. Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme, 44(7), 774–782. https://doi.org/10.1139/apnm-2018-0622

32. Lee, J.-G., Yon, J.-M., Lin, C., Jung, A. Y., Jung, K. Y., & Nam, S.-Y. (2012). Combined treatment with capsaicin and resveratrol enhances neuroprotection against glutamate-induced toxicity in mouse cerebral cortical neurons. Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association, 50(11), 3877–3885. https://doi.org/10.1016/j.fct.2012.08.040

33. Joung, E.-J., Li, M.-H., Lee, H. G., Somparn, N., Jung, Y. S., Na, H.-K., … Surh, Y.-J. (2007). Capsaicin induces heme oxygenase-1 expression in HepG2 cells via activation of PI3K-Nrf2 signaling: NAD(P)H:quinone oxidoreductase as a potential target. Antioxidants & Redox Signaling, 9(12), 2087–2098.

https://doi.org/10.1089/ars.2007.1827

34. Jolayemi, A. T., & Ojewole, J. a. O. (2013). Comparative anti-inflammatory properties of Capsaicin and ethyl-aAcetate extract of Capsicum frutescens linn [Solanaceae] in rats. African Health Sciences, 13(2), 357–361. https://doi.org/10.4314/ahs.v13i2.23

35. Shin, Y.-H., Namkoong, E., Choi, S., Bae, J.-S., Jin, M., Hwang, S.-M., … Park, K. (2013). Capsaicin regulates the NF-κB pathway in salivary gland inflammation. Journal of Dental Research, 92(6), 547–552. https://doi.org/10.1177/0022034513487376

36. Tang, J., Luo, K., Li, Y., Chen, Q., Tang, D., Wang, D., & Xiao, J. (2015). Capsaicin attenuates LPS-induced inflammatory cytokine production by upregulation of LXRα. International Immunopharmacology, 28(1), 264–269. https://doi.org/10.1016/j.intimp.2015.06.007

37. Kim, C.-S., Kawada, T., Kim, B.-S., Han, I.-S., Choe, S.-Y., Kurata, T., & Yu, R. (2003). Capsaicin exhibits anti-inflammatory property by inhibiting IkB-a degradation in LPS-stimulated peritoneal macrophages. Cellular Signalling, 15(3), 299–306. https://doi.org/10.1016/s0898-6568(02)00086-4

38. Chen, C.-W., Lee, S. T., Wu, W. T., Fu, W.-M., Ho, F.-M., & Lin, W. W. (2003). Signal transduction for inhibition of inducible nitric oxide synthase and cyclooxygenase-2 induction by capsaicin and related analogs in macrophages. British Journal of Pharmacology, 140(6), 1077–1087. https://doi.org/10.1038/sj.bjp.0705533

39. Meeran, S. M., & Katiyar, S. K. (2008). Cell cycle control as a basis for cancer chemoprevention through dietary agents. Frontiers in Bioscience-Landmark, 13(6), 2191–2202. https://doi.org/10.2741/2834

40. Kamaruddin, M. F., Hossain, M. Z., Mohamed Alabsi, A., & Mohd Bakri, M. (2019). The Antiproliferative and Apoptotic Effects of Capsaicin on an Oral Squamous Cancer Cell Line of Asian Origin, ORL-48. Medicina, 55(7), 322. https://doi.org/10.3390/medicina55070322

41. Qian, K., Wang, G., Cao, R., Liu, T., Qian, G., Guan, X., … Wang, X. (2016). Capsaicin Suppresses Cell Proliferation, Induces Cell Cycle Arrest and ROS Production in Bladder Cancer Cells through FOXO3a-Mediated Pathways. Molecules, 21(10), 1406. https://doi.org/10.3390/molecules21101406

42. Wu, D., Jia, H., Zhang, Z., & Li, S. (2020). Capsaicin suppresses breast cancer cell viability by regulating the CDK8/PI3K/Akt/Wnt/β-catenin signaling pathway. Molecular Medicine Reports, 22(6), 4868–4876. https://doi.org/10.3892/mmr.2020.11585

43. Chen, D., Yang, Z., Wang, Y., Zhu, G., & Wang, X. (2012). Capsaicin induces cycle arrest by inhibiting cyclin-dependent-kinase in bladder carcinoma cells. International Journal of Urology: Official Journal of the Japanese Urological Association, 19(7), 662–668. https://doi.org/10.1111/j.1442-2042.2012.02981.x

44. Le, T.-D., Jin, D., Rho, S. R., Kim, M. S., Yu, R., & Yoo, H. (2012). Capsaicin-induced apoptosis of FaDu human pharyngeal squamous carcinoma cells. Yonsei Medical Journal, 53(4), 834–841. https://doi.org/10.3349/ymj.2012.53.4.834

45. Islam, A., Su, A. J., Zeng, Z.-M., Chueh, P. J., & Lin, M.-H. (2019). Capsaicin Targets tNOX (ENOX2) to Inhibit G1 Cyclin/CDK Complex, as Assessed by the Cellular Thermal Shift Assay (CETSA). Cells, 8(10), 1275. https://doi.org/10.3390/cells8101275

46. Lin, M.-H., Lee, Y.-H., Cheng, H.-L., Chen, H.-Y., Jhuang, F.-H., & Chueh, P. J. (2016). Capsaicin Inhibits Multiple Bladder Cancer Cell Phenotypes by Inhibiting Tumor-Associated NADH Oxidase (tNOX) and Sirtuin1 (SIRT1). Molecules, 21(7), 849. https://doi.org/10.3390/molecules21070849

47. Jin, J., Lin, G., Huang, H., Xu, D., Yu, H., Ma, X., … Jiang, H. (2014). Capsaicin mediates cell cycle arrest and apoptosis in human colon cancer cells via stabilizing and activating p53. International Journal of Biological Sciences, 10(3), 285–295. https://doi.org/10.7150/ijbs.7730

48. Li, Q., Wang, X., Yang, Z., Wang, H., Yang, Z., Li, S., & Zheng, X. (2010). [Induction of cell cycle arrest in bladder cancer RT4 cells by capsaicin]. Zhonghua Yi Xue Za Zhi, 90(18), 1230–1233.

49. Wong, R. S. Y. (2011). Apoptosis in cancer: from pathogenesis to treatment. Journal of experimental & clinical cancer research: CR, 30(1), 87. https://doi.org/10.1186/1756-9966-30-87

50. Amantini, C., Mosca, M., Nabissi, M., Lucciarini, R., Caprodossi, S., Arcella, A., …

Santoni, G. (2007). Capsaicin-induced apoptosis of glioma cells is mediated by TRPV1 vanilloid receptor and requires p38 MAPK activation. Journal of Neurochemistry, 102(3), 977–990. https://doi.org/10.1111/j.1471-4159.2007.04582.x

51. Xu, S., Cheng, X., Wu, L., Zheng, J., Wang, X., Wu, J., … Zhang, L. (2020). Capsaicin induces mitochondrial dysfunction and apoptosis in anaplastic thyroid carcinoma cells via TRPV1-mediated mitochondrial calcium overload. Cellular Signalling, 75, 109733. https://doi.org/10.1016/j.cellsig.2020.109733

52. Chakraborty, S., Adhikary, A., Mazumdar, M., Mukherjee, S., Bhattacharjee, P., Guha, D., … Das, T. (2014). Capsaicin-induced activation of p53-SMAR1 auto-regulatory loop down-regulates VEGF in non-small cell lung cancer to restrain angiogenesis. PloS One, 9(6), e99743. https://doi.org/10.1371/journal.pone.0099743

53. Hwang, Y. P., Yun, H. J., Choi, J. H., Han, E. H., Kim, H. G., Song, G. Y., … Jeong, H. G. (2011). Suppression of EGF-induced tumor cell migration and matrix metalloproteinase-9 expression by capsaicin via the inhibition of EGFR-mediated FAK/Akt, PKC/Raf/ERK, p38 MAPK, and AP-1 signaling. Molecular Nutrition & Food Research, 55(4), 594–605. https://doi.org/10.1002/mnfr.201000292

54. Lee, G.-R., Jang, S. H., Kim, C. J., Kim, A.-R., Yoon, D.-J., Park, N.-H., & Han, I.-S. (2014). Capsaicin suppresses the migration of cholangiocarcinoma cells by down-regulating matrix metalloproteinase-9 expression via the AMPK-NF-κB signaling pathway. Clinical & Experimental Metastasis, 31(8), 897–907. https://doi.org/10.1007/s10585-014-9678-x

55. Xu, S., Zhang, L., Cheng, X., Yu, H., Bao, J., & Lu, R. (2018). Capsaicin inhibits the metastasis of human papillary thyroid carcinoma BCPAP cells through the modulation of the TRPV1 channel. Food & Function, 9(1), 344–354. https://doi.org/10.1039/c7fo01295k

56. Feng, J., Xu, Y., Wei, Z., Xia, Y., Zhang, H., Shen, C., … Fang, Y. (2022). Capsaicin inhibits migration and invasion via inhibiting epithelial-mesenchymal transition in esophageal squamous cell carcinoma by up-regulation of claudin-3 expression. Journal of Functional Foods, 89, 104934. https://doi.org/10.1016/j.jff.2022.104934

57. Venier, N. A., Yamamoto, T., Sugar, L. M., Adomat, H., Fleshner, N. E., Klotz, L. H., & Venkateswaran, V. (2015). Capsaicin reduces the metastatic burden in the transgenic adenocarcinoma of the mouse prostate model. The Prostate, 75(12), 1300–1311. https://doi.org/10.1002/pros.23013

58. Rashwan, D. S., Abd El Hamed, M. M., El-deen, M. D., Afify, M. M., Mohamed, M. H., Mohamed, A. E. R. F., … A. Elhakim, H. K. (2022). Green Synthesis of Zinc oxide Nanocomposite Using Fusarium oxysporum and Evaluation of the Anticancer Effect on Hepatocellular Carcinoma. Egyptian Journal of Chemistry, 65(4), 197–207. https://doi.org/10.21608/ejchem.2021.91841.4361

59. A. A. Nagy, R., Mohamed, M. H., K. A. Elhakim, H., D. E. Abd El-Maksoud, M., Afify, M., Mohamed, A. E. R. F., … S. R. Khafaga, D. (2022). Anticancer effect of Sorafenib-loaded iron oxide nanoparticles and bee venom on some genes expression in hepatocellular carcinoma. Egyptian Journal of Chemistry, 0. https://doi.org/10.21608/ejchem.2022.138553.6104

60. Adetunji, T. L., Olawale, F., Olisah, C., Adetunji, A. E., & Aremu, A. O. (2022). Capsaicin: A Two-Decade Systematic Review of Global Research Output and Recent Advances Against Human Cancer. Frontiers in Oncology, 12. Retrieved from https://www.frontiersin.org/articles/10.3389/fonc.2022.908487

61. Giri, T. K., Mukherjee, P., Barman, T. K., & Maity, S. (2016). Nano-encapsulation of capsaicin on lipid vesicle and evaluation of their hepatocellular protective effect. International Journal of Biological Macromolecules, 88, 236–243. https://doi.org/10.1016/j.ijbiomac.2016.03.056

62. Lv, L., Zhuang, Y., Zhang, H., Tian, N., Dang, W., & Wu, S. (2017). Capsaicin-loaded folic acid-conjugated lipid nanoparticles for enhanced therapeutic efficacy in ovarian cancers. Biomedicine & Pharmacotherapy, 91, 999–1005. https://doi.org/10.1016/j.biopha.2017.04.097

63. evaluation-of-anticancer-potential-of-capsaicinloaded-trimethyl-chitosanbased-nanoparticles-in-hepg-hepatocarcinoma-cells-2157-7439.1000240.pdf. (n.d.). Retrieved from https://www.walshmedicalmedia.com/open-access/evaluation-of-anticancer-potential-of-capsaicinloaded-trimethyl-chitosanbased-nanoparticles-in-hepg-hepatocarcinoma-cells-2157-7439.1000240.pdf

64. De Freitas, G. B. L., De Almeida, D. J., Carraro, E., Kerppers, I. I., Martins, G. A. G., Mainardes, R. M., … Messias-Reason, I. J. T. (2018). Formulation, characterization, and in vitro/in vivo studies of capsaicin-loaded albumin nanoparticles. Materials Science and Engineering: C, 93, 70–79. https://doi.org/10.1016/j.msec.2018.07.064

65. Parashar, P., Tripathi, C. B., Arya, M., Kanoujia, J., Singh, M., Yadav, A., & Saraf, S. A. (2019). A facile approach for fabricating CD44-targeted delivery of hyaluronic acid-functionalized PCL nanoparticles in urethane-induced lung cancer: Bcl-2, MMP-9, caspase-9, and BAX as potential markers. Drug Delivery and Translational Research, 9(1), 37–52. https://doi.org/10.1007/s13346-018-0575-8

66. Sampedro, A., Ramos-Torres, Á., Schwöppe, C., Mück-Lichtenfeld, C., Helmers, I., Bort, A., … Fernández, G. (2018). Hierarchical Self-Assembly of BODIPY Dyes as a Tool to Improve the Antitumor Activity of Capsaicin in Prostate Cancer. Angewandte Chemie International Edition, 57(52), 17235–17239. https://doi.org/10.1002/anie.201804783

67. Abdelnabi, H., Alshaer, W., Azzam, H., Alqudah, D., Al-Samydai, A., & Aburjai, T. (2021). Loading of capsaicin-in-cyclodextrin inclusion complexes into PEGylated liposomes and the inhibitory effect on IL-8 production by MDA-MB-231 and A549 cancer cell lines. Zeitschrift für Naturforschung C, 76(11–12), 503–514. https://doi.org/10.1515/znc-2021-0018