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# Capsaicinoids: Multiple effects on angiogenesis, invasion and metastasis in human cancers

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## Abstract

Cancer progression is a complex multistep process comprising of angiogenesis of the primary tumor, its invasion into the surrounding stroma and its migration to distant organs to produce metastases. Nutritional compounds of the “capsaicinoid” family regulate angiogenesis, invasion and metastasis of tumors. Capsaicinoids display robust anti-angiogenic activity in both cell culture and mice models. However, conflicting reports exist about the effect of capsaicinoids on invasion of metastasis of cancers. While some published reports have described an anti-invasive and anti-metastatic role for capsaicinoids, others have argued that capsaicinoids stimulate invasion and metastasis of cancers. The present review article summarizes these findings involving the bioactivity of capsaicin in angiogenesis, invasion and metastasis of cancer. A survey of literature indicate that they are several articles summarizing the growth-inhibitory activity of capsaicinoids but few describe its effects on angiogenesis, invasion and metastasis in detail. Our review article fills this gap of knowledge. The discovery of a second generation of natural and synthetic capsaicin analogs (with anti-tumor activity) will pave the way to improved strategies for the treatment of several human cancers.

### Keywords

Capsaicinoids; angiogenesis; epithelial-to-mesenchymal transition (EMT); migration; invasion; metastasis

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7.Conflict of Interest Statement

The authors declare no conflict of interest

## Introduction

Capsaicin is the spicy ingredient found in chili peppers (*Capsicum frutescens*) or hot chili red peppers (*Capsucum annum* L) [1–3]. The term “capsaicinoid” refers to capsaicin-like compounds found in different strains of chili peppers. The amount of capsaicin present in chili peppers defines the pungency and spiciness of the chili pepper. It is generally believed that such pungent capsaicin-compounds were synthesized by the chili plants as a defense mechanism against fungi, microbes and herbivores. The majority of capsaicin is found in the placental tissue and lesser amounts have been detected in seeds and pericarp portion of *Capsicum.* The heat index of capsaicin is measured by of the Scoville scale; the higher the Scoville index, the hotter is the pepper [4, 5] .For example, the mild bell pepper has an average Scoville index of 300units, whereas the hot “orange habanero peppers” have a Scoville index of about 400,000 units (Figure 1A). Pure capsaicin gas the highest Scoville scale value of 16 million units.

Capsaicin (trans-8-methyl-N-vanillyl-6-nonemide) is a crystalline colorless odorless alkaloid (Figure1B) with the molecular formula $C_{18}H_{27}NO_3$ [6]. It is a lipophilic compound (Molecular weight =305.4g/mol) which is insoluble in water but readily soluble in non-polar solvents like ethanol and DMSO. Capsaicin displays cis-trans isomerism because the double bond prevents internal rotation [6–8]. Naturally occurring capsaicin is the cis-isoform. Apart from capsaicin, there are many naturally occurring capsaicinoids in hot peppers (*Capsicum annum* and *Capsaicum frutenscens*) namely dihydrocapsaicin, nondihydrocapsaicin, norcapsaicin, homocapsaicin and homodihydrocapsaicin [9]. Capsaicinoids are synthesized in the placenta of chili pepper fruit by enzymatic condensation (mediated by capsaicin synthase) of vanillylamine and different fatty acid side chains [1, 6, 10]. Interestingly, non-pungent capsaicin-like compounds have been isolated from Japanese CH-19 sweet papers [2, 11, 12]. These compounds are collectively called as capsinoids. The compounds in the capsinoid family include capsiate, dihydrocapsiate and nor dihydrocapsiate. Capsaicin displays a spectrum of biological activities. Traditionally, it has been used as a pain-relieving agent in patches, creams and lotions [10, 13, 14]. However, it has also shown to possess anti-inflammatory effects, antioxidant activity and anti-obesity properties [1, 2, 7, 10, 15–19]. Conflicting data exist anti-cancer activity of capsaicinoids. A majority of published reports have revealed that low doses of capsaicin suppress the growth of many types of human cancers. Capsaicin has also been found to sensitize neoplastic cells to the apoptotic activity of chemotherapeutic drugs [20–22]. However, a few research papers have shown that capsaicin has tumor-promoting activities in skin cancer, breast cancer and colon cancer [15, 23, 24]. These tumor-promoting activities were observed when high doses of capsaicin was used to treat the cancer cells. It may also be possible that the anti-neoplastic activity of capsaicin depends on the nature of the cancer; skin and colon cancers may be unique in the fact that capsaicin induces proliferative effects in these cancers. The biological activity of capsiate and its related compounds have not been studied extensively [2, 11, 12]. It seems that the bioactivity of capsiate-like compounds is similar to that of capsaicinoids. However, an advantage of capsiate (and its related compounds) is that they do not produce the “burning sensation” associated with capsaicin.

The pain-reliving activity of capsaicin is mediated by its binding to the transient receptor potential vanilloid (TRPV) superfamily of ion-channel receptors [25, 26]. Although, the TRPV family of receptors have six members (TRPV1-TRPV6) [16, 25, 26]. Several capsaicin-like compounds have been isolated and characterized from different species of chili peppers [2, 12]. Similarly, rational chemical synthesis have led to the discovery of capsaicin analogs that resemble capsaicin in their structure and bioactivity [11, 21]. These natural and synthetic capsaicin-like compounds are collectively known as capsaicinoids. All capsaicinoids are agonists of the TRPV1 receptor [27, 28]. However, recent studies have shown that some of the biological effects of capsaicinoids may be independent of TRPV receptors [29–32].

With the exception of a limited number of studies that reported that the long-term administration of capsaicin induced neoplastic changes in the liver and cecum [33], promoted the survival and growth of bladder, colon and skin cancers [15, 24, 33, 34] the overwhelming majority of published data show that capsaicin displays potent anti-tumor activity in a diverse array of human cancers [35–40]. Early research demonstrated that capsaicinoids display robust chemopreventive activities, inhibiting carcinogenesis in lung, prostate, pancreatic, breast and skin cancer [1, 38, 41–44]. Subsequently, published reports have confirmed the anti-cancer activity of capsaicin in human breast, lung, prostate, gastric, renal, oral and hepatocellular carcinoma [1, 7, 17]. The anti-cancer activity of capsaicin has been found to be mediated via TRPV-dependent, as well as TRPV-independent, mechanisms [17, 45–48]. Apart from their effects on primary tumors, capsaicinoids have been found to regulate tumor angiogenesis and metastasis; two key processes in cancer progression. There are several in-depth review articles describing the growth-inhibitory activity of capsaicinoids. However, there is a paucity of reviews which systematically document the effect of capsaicinoids on tumor angiogenesis, epithelial-to mesenchymal transition (EMT), invasion and metastasis. The present article fills this void of knowledge. The first portion of this manuscript describes the anti-angiogenic activity of capsaicinoids in tumor angiogenesis. Subsequently, we discuss the bioactivity of capsaicinoids on the individual steps of the metastatic cascade, namely EMT, migration and invasion. Finally, we describe the therapeutic applications of capsaicin in controlling cancer pain in patients.

## 1. Capsaicinoids and Angiogenesis

Angiogenesis refers to the growth of new blood vessels from pre-existing vasculature. It is a complex multistep process involving endothelial cell activation, cell proliferation, invasion, chemotactic migration and differentiation into new blood vessels[49]. The acquisition of an angiogenic phenotype is considered to be a vital step in tumor progression [50, 51]. Tumors need to recruit blood vessels in order to obtain oxygen and nutrients necessary for their growth, as well as to dispose of metabolic waste products. Furthermore, endothelial cells secrete growth factors which stimulate tumor growth in an autocrine and paracrine manner [52, 53]. The onset of angiogenesis coincides with increased entry of neoplastic cells into circulation and thus facilitates metastasis [50, 54]. Several congruent studies indicate that the transition from an *in situ* carcinoma to invasive cancer (for solid tumors) must be accompanied by neovascularization. Therefore, the suppression of angiogenesis is a highly

effective strategy for the treatment of multiple cancers [52, 55, 56], one for which capsaicinoids may have relevant therapeutic potential.

Min et al., (2004) studied the effects of capsaicin on angiogenesis using multiple model systems [57]. They observed that capsaicin suppressed vascular endothelial growth factor (VEGF)-induced angiogenesis in Matrigel model systems, *ex vivo* rat aortic rings models, chicken chorioallantoic membrane (CAM) models[35] and *in vivo* Matrigel plug experiments [57]. Capsaicin robustly inhibited VEGF-induced endothelial cell proliferation and invasion [57]. Similarly, the non-pungent capsinoids, capsiate and dihydrocapsiate inhibited VEGF-induced angiogenesis in both cell culture and mouse models [58]. Capsiate and dihydrocapsiate inhibited VEGF-induced endothelial permeability and formation of cell-cell junctions[59] . The anti-angiogenic activity of capsiate and dihydrocapsiate was found to be independent of the TRPV1 receptor [58]. In fact, the activation of the TRPV1 receptor by another capsaicin-like compound, evodiamine (derived from tetradium or bee tree), stimulates angiogenesis in Matrigel Plug model [60]. The pro-angiogenic activity of evodiamine was studied in human aortic endothelial cells (HAEC) in the context of cardiovascular disease and involved activation of the nitric oxide pathway [60]. Min et al., (2004) observed that capsaicin suppressed VEGF-induced angiogenesis by a mechanism distinct from the activation of KDR/Flk-1 VEGF receptor [61, 62]. The anti-angiogenic activity of capsaicin correlated with decreased expression of cyclin D1, which in turn translated to decreased phosphorylation of Rb, leading to G1 arrest of human umbilical cord endothelial cells (HUVEC)[57]. Furthermore, capsaicin also suppressed VEGF-induced activation of focal adhesion kinase (FAK) and p38 kinase (Figure 2 )[57]. Molecular docking studies showed that capsaicin and capsiate could directly bind to Src kinase in a hydrophobic cleft near the ATP binding site [58]. However, the authors did not confirm the results of molecular modeling by binding experiments showing a direct association between capsaicin and Src.

Conflicting reports exist on the effect of capsaicin on the expression of the angiogenic growth factor VEGF. Patel et al., (2002) showed that capsaicin enhanced VEGF levels by increasing the DNA binding activity of hypoxia inducible factor alpha (HIF-1α) on the VEGF promoter in human melanoma cells [63]. In contrast, subsequent studies showed that capsaicin suppressed production of VEGF from myeloma and non-small lung cancer (NSCLC) cells [64, 65]. Chakraborty et al., (2014) showed that capsaicin decreased VEGF secretion via the p53-scaffold matrix-associated region-1 (SMAR1) pathway in NSCLC cells [65]. The anti-angiogenic activity of capsaicin was mediated by stabilization of p53 (mediated by upregulation of SMAR1) and subsequent degradation of HIF-1α, resulting in decreased transcription of VEGF. The question arises whether the conflicting observations were due to cell type or capsaicin. Furthermore, the treatment of human NSCLC with capsaicin induced repression of cyclooxygenase-2 (COX-2) activity and production of prostaglandin-2 ($PGE_2$), which in turn blocked nuclear localization and transcriptional activation of HIF-1α, causing decrease in VEGF production [65]. Such conflicting results involving the effect of capsaicin on VEGF production may be explained by differences in the type of human cancer (melanoma versus myeloma and NSCLC) being used in the studies.

## 2. Capsaicinoids and Epithelial-to-Mesenchymal Transition (EMT)

The ability of neoplastic cells to travel away from the primary tumor to distant sites is essential for metastasis. EMT is believed to be one of the initial steps of metastasis and refers to the trans-differentiation of epithelial cells to motile mesenchymal cells [66, 67]. The process of EMT also confers epithelial neoplastic cells with increased invasiveness and the ability to degrade the extracellular matrix proteins [66]. The EMT program is not a binary on/off switch transitioning cells from the epithelial to the mesenchymal phenotype[67, 68], but rather a spectrum of molecular changes in which intermediate mixed epithelial/mesenchymal phenotypes [69, 70] have been detected (Figure 3). The acquisition of EMT coincides with loss of epithelial biomarkers like E-cadherin, beta-catenin, Zona occudens-1 (ZO-1) and increased expression of mesenchymal proteins like fibronectin, vimentin and N-cadherin[67, 71, 72]. Such molecular changes are regulated by specific EMT-transcription factors like Twist, [73, 74] Snail, Slug [75] and Zeb1[76]. Other transcription factors like Zeb2, Foxc2, Prrxl (and many others) have also been shown to be capable of inducing a subset of the EMT process [67, 71].

The effect of capsaicin on EMT is controversial. Yang et al., (2013) treated SW480 human colon cancer cells with 100 μM capsaicin for 48 hours. Subsequently, they analyzed the cell lysates for EMT-biomarkers [77]. They observed that capsaicin decreased the expression of E-cadherin and increased the levels of mesenchymal proteins like vimentin and N-cadherin. Taken together, capsaicin promoted EMT in SW480 cells at a high concentration of 100μM [77]. Capsaicin also increased the expression of matrix metalloproteinase (MMP)-2 and MMP-9 suggesting that it endowed pro-migratory and pro-invasive properties on human colon cancer cells. Furthermore, the treatment with HCT-116 human colon cancer cells with 1–10 μM capsaicin led to induction of the EMT program [77]. Geng et al., (2016) observed that high doses of capsaicin (50 mg capsaicin/kg body weight administered intragastrically) promoted EMT in the urethane-induced lung carcinogenesis [78] model. Immunohistochemical (IHC) analysis showed a decrease in E-cadherin with concomitant increase in N-cadherin in the lungs of mice administered with capsaicin [78]. A drawback of these studies is that the authors only analyzed one epithelial protein and one mesenchymal biomarker. As mentioned above, data from several research labs have highlighted the existence of a “partial EMT” state where the cells retain a mixture of epithelial and mesenchymal traits [67, 68, 71, 79]. Therefore, analysis of a panel of epithelial and mesenchymal proteins would have enabled the authors to better characterize capsaicin-induced EMT in the lung carcinogenesis model.

The EMT-inhibitory activity of capsaicin was studied in human cholangiocarcinoma cells. Wutka et al., (2014) observed that capsaicin suppressed EMT in two cholangiocarcinoma cell lines (SZ-1 and TFK-1) in a time- and concentration-dependent manner [80]. Two concentrations of capsaicin (150 μM and 200 μM) increased the expression of E-cadherin with concomitant decrease in mesenchymal protein vimentin levels in both cell lines. The maximal suppression of EMT by capsaicin was achieved 48–96 hours post treatment [80]. Notably, capsaicin decreased the levels of N-cadherin in SZ-1 cells, but not in TFK-1 cells. Such observations show that the effects of capsaicin on EMT are critically dependent on the nature of the cell line used. Capsaicin blocked EMT in TSGH, 5637 and T24 human bladder

cancer cells. The EMT-inhibitory activity of capsaicin correlated to the inhibition of tumor associated NADH oxidase (tNOX) levels in TSGH and T24 cells [81]. Innovative studies by Amatini et al., (2016) showed that high doses of capsaicin may induce capsaicin-resistance (CPS-R) in human bladder cancer cells [82]. A subset of cells survive the high concentrations of capsaicin by undergoing autophagy. These CPS-R bladder cancer cells display typical mesenchymal morphology along with overexpression of mesenchymal biomarkers like vimentin, EMT transcription factors Zeb 2, α5-, β1-integrin subunits and integrin-like kinase [82]. Further support for the EMT-inhibitory activity of capsaicin was provided by Xu et al.,(2018) who observed that capsaicin downregulated the expression of EMT transcription factors Snail1, Twist1, as well as MMP-2 and 9 in human thyroid carcinoma cells[83]. Capsaicin-induced suppression of Twist1 and MMP-9 was abrogated by the TRPV1 antagonist capsazepine, suggesting that the TRPV1 receptors played an integral role in the anti-EMT activity of capsaicin in thyroid carcinoma cells[83]. Dai et al., (2018) measured the growth-inhibitory activity of a combination of capsaicin and sorafenib in hepatocellular cancers[84]. They observed that the combination of 80 μM capsaicin and 4 μM sorafenib suppressed the induction of EMT better than either drug given alone[84]. There was a robust upregulation of E-cadherin and concomitant decrease of N-cadherin and vimentin in the cancer cells treated with a combination of capsaicin and sorafenib [84]. These observations suggest that capsaicin sensitizes human cancer cells to the anti-EMT activity of standard chemotherapeutic drugs used in the clinic.

## 3. Capsaicinoids and tumor migration, invasion

The migration and invasion of cancer cells into the surrounding stroma, blood vessels and lymph nodes is a vital step in the metastatic pathway [85, 86]. Cell migration measures the ability of cells to travel under the influence of chemotactic gradient. Cell invasion measures the ability of cells to degrade basement membrane proteins and subsequently migrate in response to chemotactic stimuli. Conflicting reports exist on the impact of capsaicin on tumor cell migration and invasion. Data by Yang et al., (2013) also show that capsaicin stimulates the invasion of human colon carcinoma cells via the Akt/mTOR and STAT-3 dependent pathways [77]. Aside from the research paper of Yang et al. (2013), the bulk of published reports show that capsaicin displays anti-migratory and anti-invasive activity in breast cancer, melanoma, thyroid cancer, bladder cancer, small cell lung cancer (SCLC) and cholangiocarcinoma[80–83, 87, 88]. The anti-migratory and anti-invasive activity of capsaicin in thyroid cancer was found to be mediated via a TRPV1-dependent mechanism [83]. Caprodossi et al., (2011) studied the impact of TRPV1 status on the invasion-regulatory properties of capsaicin[89]. They observed that capsaicin increases the invasion of TRPV1-null 5637 human bladder cancer cells. The pro-invasive activity of capsaicin coincides with increased production of insulin growth factor (IGF-1), granzyme A (GZMA) and activation of MMP-9 in the TRPV-null cells. Furthermore capsaicin induced cytoskeletal remodeling in 5637 cells[89]. Gene expression analysis showed that capsaicin elevated the levels of pro-angiogenic genes like angiopoietins, VEGF, MMP1, MMP-1, tissue inhibitor of matrix metalloproteinase 1 (TIMP1), NM23A and S100A in TRPV1-null cells[89]. Finally, the authors re-expressed TRPV1 in 5637 cells by transient transfection and subsequently treated the cells with 100 μM capsaicin[89]. They observed that capsaicin displayed anti-invasive and growth-inhibitory activity in TRPV1+/+ 5637 cells[89]. Therefore, the loss of

TRPV1 causes capsaicin to promote invasion, whereas its re-expression has the opposite effect. These findings align well with clinical observations that high grade invasive bladder cancers display decreased TRPV1 expression relative to low grade tumors [90, 91]. The differential TRPV1 expression may, at least, in part explain the conflicting data involving the effects of capsaicin on tumor invasion. It is tempting to speculate that the status of TRPV receptors on neoplastic cells may play a role in the pro-invasive versus anti-invasive activity of capsaicin in human cancers.

Capsaicin recruits multiple signaling mechanisms to regulate migration and invasion. These include activation of EMT, AMP activated protein kinase (AMPK), MMP signaling pathway, elevation of intracellular calcium, VEGF, regulation of Wnt-Hedgehog, tNOX, Akt, MMPs and inhibition of epidermal growth factor receptor (EGFR), ERK, p38 MAP kinase, Rac1, NF-kB, AP-1[80–83, 87, 88]. Apart from its bioactivity as a single agent, capsaicin synergizes with established chemotherapeutic drugs to potently suppress the migration and invasion of tumor cells. Dai et al., (2018) investigated the combinatorial anti-migratory and anti-invasive activity of capsaicin and sorafenib was in LM3 hepatocellular carcinoma cells. Wound healing migration assays showed that the combination of 80 μM capsaicin and 4 μM sorafenib suppressed migration to a greater magnitude than either sorafenib or capsaicin alone[84]. The abovementioned drug combination also suppressed invasion of LM3 cells. The combination of 80 μM capsaicin and 4 μM sorafenib inhibited the induction of EMT and decreased levels of MMP-2 and MMP-9 (in LM3 cells) better than either drug used alone[84]. Studies by Wang et al., (2018) explored the anti-invasive activity of the combination of cisplatin and capsaicin in human osteosarcoma cells. The authors chose to study the anti-invasive activity of cisplatin and capsaicin in three osteosarcoma cell lines namely MG63, 143B and HOS cells [92]. The combination of 16.7 μM cisplatin and 100 μM capsaicin suppressed invasion (in all the three cell lines more robustly than either agent administered alone [92]. The anti-invasive activity of capsaicin and cisplatin was associated with decreased expression and activity of MMP-2 and MMP-9. The combination of capsaicin and cisplatin resulted in the greatest magnitude of reduction of MMP2 and MMP9 expression (and activity) relative to the drugs as single agents [92].

While the majority of studies have focused on the use of capsaicin as an anti-cancer agent, the clinical development of capsaicin as anti-cancer drug is problematic due to its unfavorable side effect profile. Several convergent studies have shown that systemic administration of capsaicin in humans leads to intense gut pain, hyperalgesia, stomach cramps and nausea. Clinical studies show that these adverse side effects have led patients to abandon taking the oral capsaicin [10, 93–95]. This drawback can be circumvented by the discovery of capsaicin analogs, which retain the anti-tumor activity of capsaicin but do not produce the “heat-sensation” of capsaicin. Structure Activity Relationship (SAR) studies show that the structure of capsaicin can be divided into three pharmacophore-regions namely Region A, B, and C (Figure 4) [96]. The addition of long chain unsaturated fatty acyl groups to the Region C of capsaicin generates non-pungent capsaicin analogs[96]. Studies in our laboratory compared the anti-invasive activity of capsaicin and two capsaicin analogs arvanil and olvanil in human SCLC [87]. Arvanil and olvanil showed better anti-invasive activity than capsaicin in a panel of human SCLC cell lines. The anti-invasive activity of arvanil and olvanil was independent of TRPV1 and mediated by activation of the AMPK pathway [87].

Lee et al., (2017) investigated the anti-invasive activity of the capsaicin analog capsazepine in human prostate cancer cells [97]. They observed that capsazepine robustly suppressed the invasion of DU145 human prostate cancer cells via inhibition of the JAK/STAT3 pathway.

## 4. Capsaicinoids and Metastasis

Initial research studied the impact of the sensory effects of capsaicin on tumor metastasis [14, 98]. The administration of high doses of capsaicin causes deactivation of sensory neurons[10]. Erin et al. (2004), used high doses of capsaicin (125 mg capsaicin/kg body weight) to ablate the activity of systemic sensory neurons and studied the effects of such denervation on the metastasis of mammary cancers [23]. The authors used the orthotopic 4T1 syngeneic mouse model of metastasis in their studies. The mice were pretreated with 125mg capsaicin/kg bodyweight (injected subcutaneously into the fat tissues if the neck0 for two consecutive days, designated as day 1 and 2 of the study [23]. 4T1 murine mammary carcinoma cells were orthotopically injected into the right axillary mammary fat pad 7–21 days after the administration of capsaicin. The inactivation of sensory neurons (by capsaicin) promoted the metastasis of mammary tumors to the lungs and heart. Notably, the high doses of capsaicin did not affect the growth rate of the primary tumor [23]. A subsequent published report by the same research group compared gene expression patterns (in the primary tumors) between the vehicle-treated and capsaicin-treated mice [99]. They identified a group of seventeen genes that were decreased in primary tumors of capsaicin treated mice versus vehicle treated mice. Interestingly, all seventeen identified genes regulate growth, differentiation and progression of human cancers [99].

Yang et al., (2013) investigated the effect of capsaicin on the metastasis of CT26 murine colorectal carcinoma cells [77]. They treated CT26 cells with 100μM capsaicin for 48 hours and then intravenously injected these cells in mice. After 15 days, and their lungs of mice were examined for metastatic nodules [77]. The authors observed that CT26 treated with 100μM capsaicin produced a greater number of lung metastatic nodules than vehicle-treated mice. A noteworthy aspect of this study was that CT26 cells were pretreated with a rather high concentration of capsaicin (100μM) prior to being injected in mice [77]. Another important point was that the authors did not use orthotopic models to measure metastasis. They injected the CT26 cells directly into the tail vein of mice, which is not a true representation of metastasis, since it circumvents important events of the metastatic pathway like migration, EMT and invasion of cancer cells [77].

Venier et al. (2015) studied the anti-metastatic activity of capsaicin in the transgenic TRAMP model of prostate cancer [100]. The authors administered 5 mg capsaicin/kg body weight by oral gavage three times a week. The administration of capsaicin significantly lowered metastatic burden in TRAMP mice model. The capsaicin-treated mice had also higher non-cancerous intraepithelial neoplasia (PIN) relative to the control group. IHC experiments showed an elevation of the tumor suppressor p27Kip1 in the tumors of capsaicin-treated TRAMP mice. This study seems to suggest that capsaicin may possess robust anti-metastatic activity [100]. A recent publication by Kandagalla et al., (2019) used computational approaches to determine the impact of capsaicin on TGF-β-induced

metastasis [101]. They observed that capsaicin targets several key genes in the TGF-β signaling pathway [101].

## 5. Capsicinoids and Cancer Pain

The occurrence of pain is a common symptom of cancer patients, especially those who present with advanced or terminal disease. It is estimated that over 70% of cancer patients experience pain during and after their treatment [102, 103]. Chemotherapy-induced peripheral neuropathy along with chronic pain is often observed in cancer patients. A diverse array of chemotherapeutic drugs like taxol, vincristine, oxaliplatin and bortezomib induce peripheral neuropathy in patients [104]. The pain-relieving activity of capsaicin is mediated by the TRPV1 receptor [25–27]. Although, acute exposure to capsaicin activates theTRPV1 receptor causing a burning sensation, prolonged exposure to capsaicin desensitizes TRPV1 and produces relief from pain. Another approach has been to explore the pain-relieving activity of TRPV1 antagonists [4, 7, 8, 10, 13, 14, 16, 105].

Quetenza is a high dose 8% capsaicin patch (also called NGX-4010) has been found to decrease neuropathic pain after a single application within an hour for about 12 weeks. Each NGX-2010 patch contains 179 mg of capsaicin [4, 10]. Anand et al. (2019) examined the effect of the Quentenza patch on sixteen patients suffering from chemotherapy-induced peripheral neuropathy (CIPN). The patients were administered the capsaicin patch on their feet for 30 minutes for a total period of there months [104]. The study found that patients reported a decrease in spontaneous pain, touch-induced pain and cold-evoked pain. After the treatment period, a skin biopsy was done in both the placebo and capsaicin-treated group of patients. The skin biopsies from placebo-treated patients showed loss of intra-epidermal and sub-epidermal nerve fibers. In contrast, the skin biopsies from capsaicin-treated patients showed a significant increase (towards normalization) of intra-epidermal and sub-epidermal nerve fibers [104]. Additionally, levels of key signaling proteins like nerve growth factor, Neurotrophin-3 were normalized in the capsaicin–treated patients. Taken together, the NGX-2010 capsaicin patch provides relief from chronic cancer pain and accelerates regeneration of sensory nerve fibers.

A prevalent side effect of chemotherapy and radiation therapy is the high incidence of oral mucositis (painful ulcers in the throat and oral cavity) in patients [106, 107]. Currently, there are no therapies to relieve the pain of these lesions. Berger et al., (1995) investigated the potential of capsaicin to diminish the pain caused by oral mucositis. They administered 5–9ppm capsaicin (as cayenne peppers) in candy. They made two strengths of capsaicin-candy, the first one contained 5–9ppm capsaicin and second contained half the amount of capsaicin [108]. The study was performed in 11 patients and all of them reported pain relief after using the capsaicin-containing candy. The capsaicin candies did not totally abolish the pain but minimized the discomfort due to oral mucositis [108]. Out of the eleven patients two opted for candies containing half the dose of capsaicin. The authors observed that even candies containing lower doses of capsaicin provided substantial pain relief to the patients [108].

A relatively rare side effect of cancer treatment is long term postsurgical neuropathic pain. Surgical resection of the tumor may cause transection, contusion, stretching, or inflammation of the nerves, producing chronic pain symptoms in the patient [109]. Early

studies by Watson et al, (1989) investigated the effect of 0.025% capsaicin cream on post-mastectomy pain in eighteen patients. Their data reveal that 12 out of the 18 patients experienced a 50% (or greater) relief in their pain symptoms [110]. Such observations were in alignment with the findings of Dini et al., (1993) who tested the pain-relieving activity of 0.025% capsaicin cream in 21 patients suffering from post-mastectomy pain [111]. They observed that 58% of the patients receiving capsaicin cream experienced a substantial reduction in pain. Eleven of the thirteen responding patients continue to experience improvement in pain symptoms for three months after of stopping topical-capsaicin therapy

Ellison et al. (1997) explored whether the topical administration of capsaicin cream could alleviate postsurgical neuropathic pain. The study was performed in 99 patients who had undergone surgical procedures namely mastectomy, thoracotomy, amputation or any surgical procedure as part of their cancer treatment regimen [112]. After randomization, the treatment group received 0.075% capsaicin cream to be applied 4 times every day for a period of 8 weeks. The authors observed that 0.075% capsaicin caused initial adverse reactions like burning sensation and redness of skin as well as more coughing in patients. The number of patients who decided to discontinue the cream was similar to that of the placebo group indicating that capsaicin was well tolerated in patients. At the end of study 60% of patients (in the capsaicin-treated) group reported pain-relief relative to 18% in the placebo-cream-treated patients [112]. Capsaicin-induced pain relief was maximal at the end of 4 weeks and remained constant thereafter.

The capsaicinoid resiniferatoxin (RTX) has been observed to display potent analgesic activity in several animal models [113]. Mendez et al. (2006) examined the analgesic effect of RTX in mice models of osteosarcoma. NCTC-2472 murine osteosarcoma cells were injected into the tibial medullar cavity to induce osteosarcoma in mice [114]. The subcutaneous injection of a single dose of RTX (0.01–0.1mg/kg bodyweight) inhibited osteosarcoma-induced hyperalgesia in a dose-dependent manner. The pain-relieving activity of RTX (administered via intrathecal injection) was also observed in canine models of spontaneous osteosarcoma [115, 116]. The pathophysiology of canine osteosarcoma resembles human bone cancers. The results obtained in these mice and canine models has formed the basis of a Phase 1 clinical trial involving intrathecal RTX injections to relieve cancer pain in patients. The trial is still ongoing but preliminary results show that patients experience improvement in pain symptoms after RTX treatment [113].

The TRPV1 receptor is known to play a vital role in stimulating pain symptoms in arising from heat, acidosis and extracellular protons [26]. Tumors progression occurs in an acidotic environment [117]. This raises to the possibility that disruption of TRPV1 function by TRPV1 antagonists may alleviate pain symptoms. Several research papers have shown that the capsazepine or ABT102 potently decreases pain symptoms in mouse models of bone cancer [114, 118]. TRPV1 antagonists like capsazepine and SB366791 potentiate the pain relieving activity of cannabinoid drugs and morphine [119–122]. The administration of TRPV1 antagonists did not cause discomfort or gross toxicity to mice. Such studies will facilitate the development of TRPV1-based pain relieving drugs in human cancers.

### 6. Conclusions and Future Directions

A survey of literature show that conflicting reports exist on the effect of capsaicin on invasion, EMT and metastasis. A noticeable caveat of the majority these studies is that they have been mostly done with high concentrations of capsaicin in cell culture systems and not in animal models. Such facts underscore the need for further in-depth studies in animal models to precisely delineate the effects of capsaicin on the EMT, migration, invasion and metastasis of human cancers. Several model systems have shown that capsaicin and capsiate inhibit VEGF-induced angiogenesis activity in endothelial cells. The treatment of capsaicin causes robust downregulation of the angiogenic growth factor VEGF in myelomas and NSCLC. All these findings suggest that capsaicin is an anti-angiogenic nutritional compound. An important biological activity of capsainoids is their ability to relive cancer pain symptoms. The combination of capsaicinoids with standard chemotheraputic drugs has a two-fold advantage. Firstly, capsaicinoids may potentiate the activity of chemotherapy and second it may provide pain relief for cancer patients

An exciting development in the field of capsaicin-based drug design has been the discovery of non-pungent capsaicin-analogs which retain the anti-tumor activity of capsaicin. It is hoped that future studies will identify a new generation of capsaicin mimetics with potent anti-metastatic activity in human cancers.

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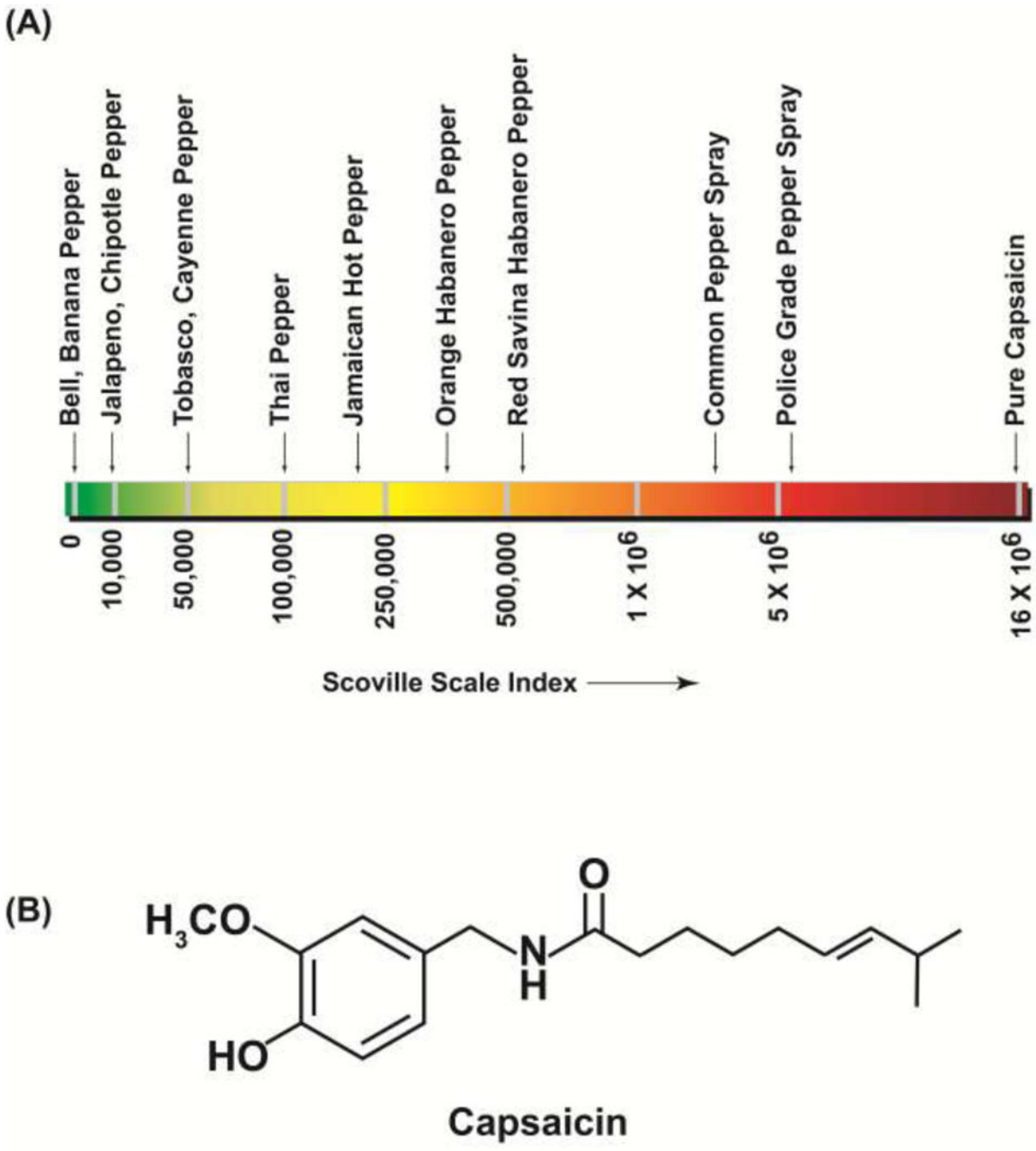


**Figure 1.**

The hotness and pungency of chili peppers is measured by the Scoville scale. The higher the Scoville unit, the more “spicy and pungent” the pepper. Pure Capsaicin has the highest Scoville index and bell peppers have the lowest Scoville value.

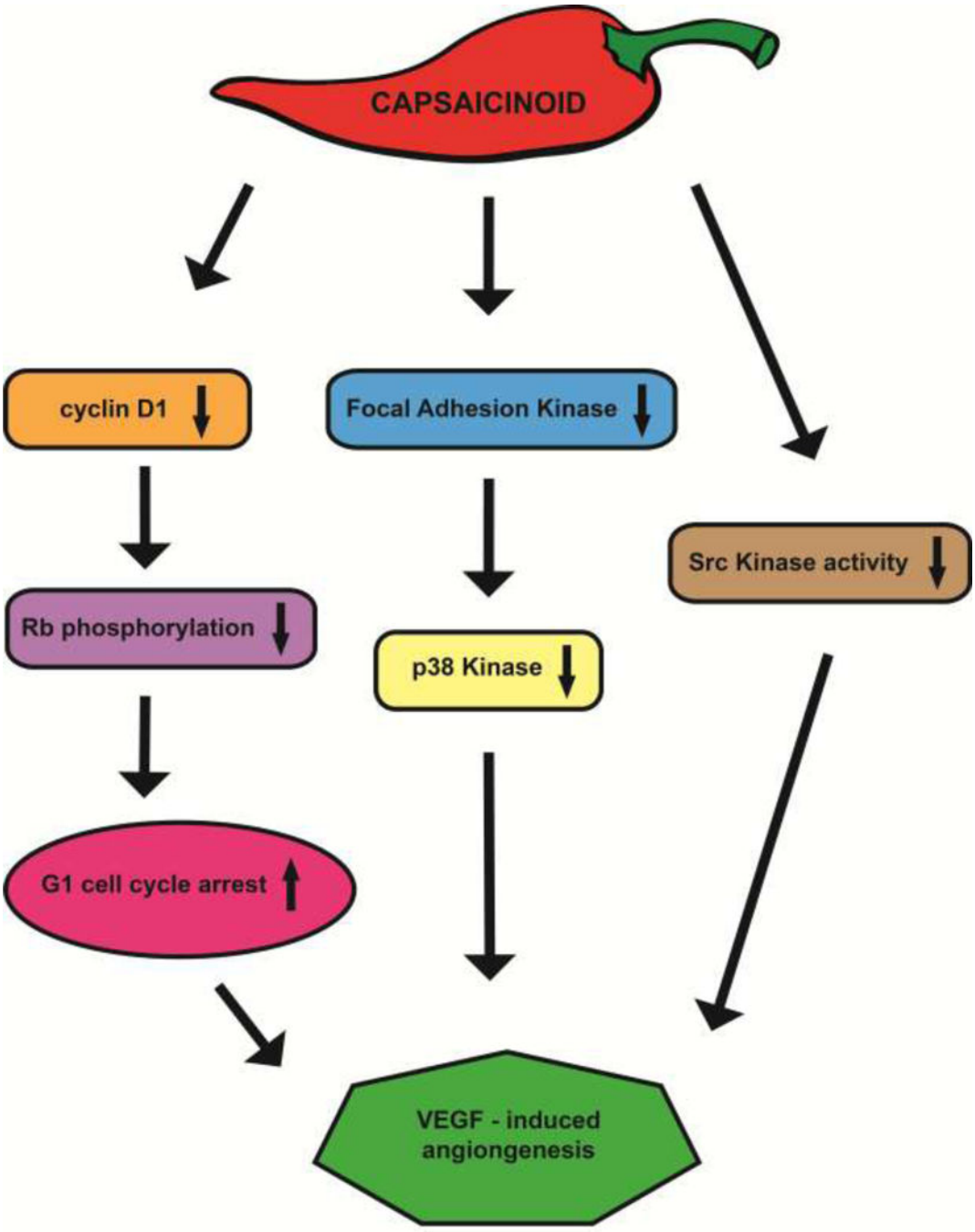


**Figure 2.**
A flow chart representing the signaling pathways by which capsaicinoids suppress VEGF-induced angiogenesis.

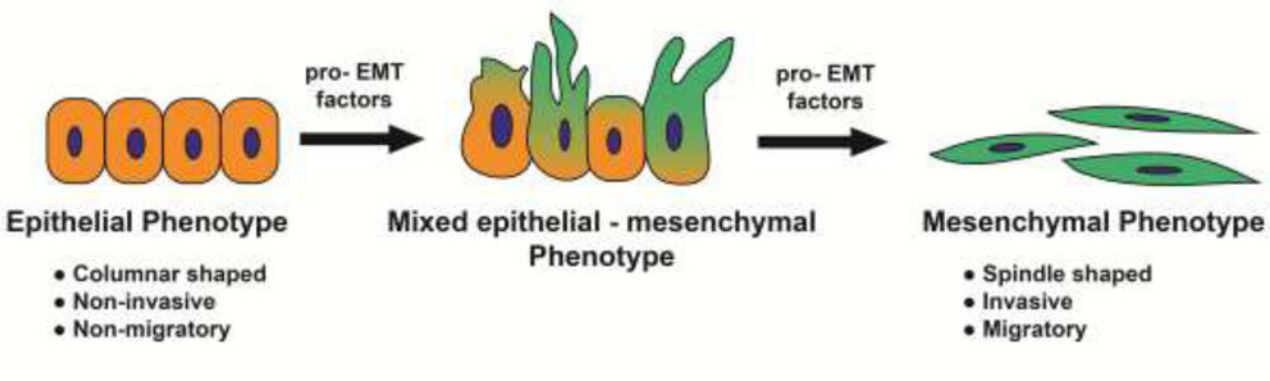


**Figure 3.**

A simplified schematic of epithelial-to-mesenchymal transition in human cancer cells. The induction of EMT is a spectrum of biochemical mechanisms where epithelial, mesenchymal and mixed epithelial-mesenchymal phenotypes are observed.

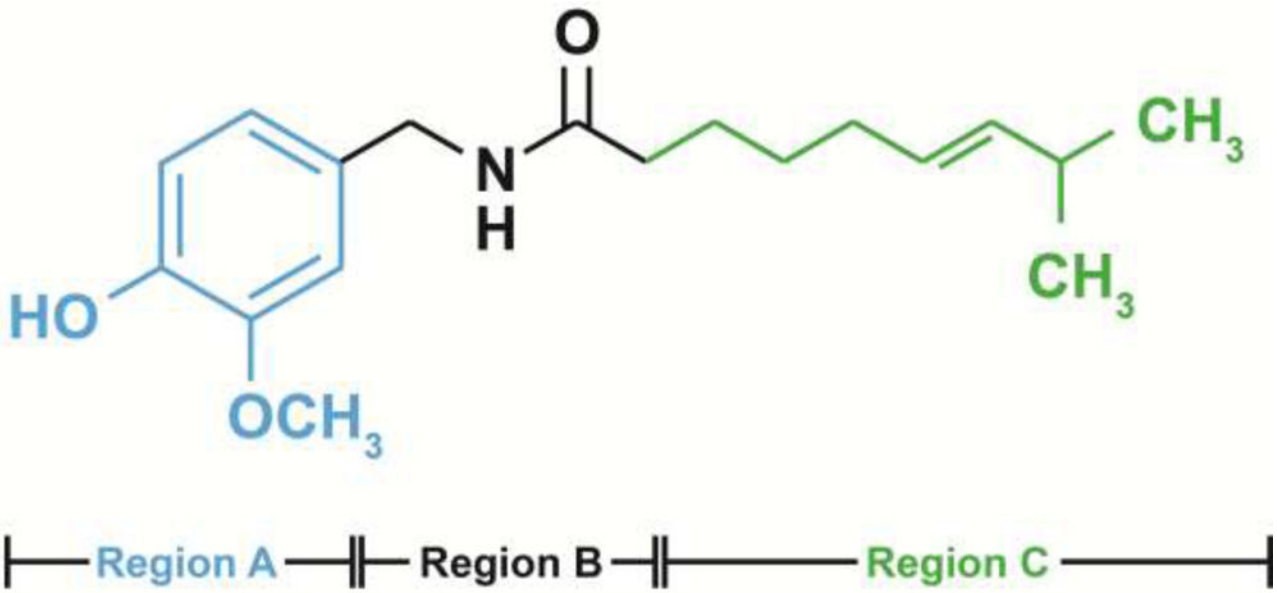


**Figure 4.**

Structure of capsaicinoids. The blue structural moiety represents Region A; the red portion of the structure represents Region B; the green alkyl side chain represents Region C.