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Capsaicin as a Cancer Chemopreventer- The Two Sides of the Same Coin

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Review Article

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Abstract

The pungent component of the chili pepper known as capsaicin is popular both as a spice and as a carcinopreventer. In vitro experiments and studies with animal models suggest that capsaicin may inhibit gastrointestinal, pancreatic, hepatic and other sorts of cancer development through a number of different pathways. Additionally, capsaicin may improve the therapeutic potential of traditional anti-cancer medications when taken with them. However, several reports have raised concerns that capsaicin may have a dual impact on cancer cells that promotes both cell proliferation and metastatic abilities. The purpose of this review is to examine the contradicting information regarding capsaicin's ability to prevent cancer.

Keywords: Capsaicin; Cancer; Carcinopreventer; Cancer Promoter

Abbreviations: NF-kB: Nuclear Factor-kappa B; TRPV: Cation Channel Family Member; ROS: Reactive Oxygen Species; STATS: Transition Activator Protein; BCRP/Abcg2: Breast Cancer Resistance Protein; STAT and JAK: Signaling Pathway; CDK: Cyclin Dependent Kinase; PTEN: Tensin Homolog; HK: Hexokinase; TRPV: Transient Receptor Potential Vanilloid ; P53: Tumor Suppressor Gene; Bcl-2: Apoptosis Regulator; Bax : A Bcl Family Member; tNOX : Tumor-Associated NADH Oxidase; TGF-β: Transforming Growth Factor-beta; SMADA4: Signal Transduction Protein; AMPK: Adenosine Monophosphate Protein Kinase; PPAR: Peroxisome Proliferator Activator Gamma; DMH: 1,2-domethyl-hydrazine;ATF: Activated Transcription Factor;SIRT1/SOX2 pathway; ERK: Extracellular Regulatory Kinases; E2F: transcription factors; PARP: Poly (ADP-ribose) Polymerase.

Introduction

Capsaicin, the main phytochemical found in chili and red peppers, has a long history in both ordinary culinary use and traditional medicine due to its powerful pungent and health effects. Analgesic, anti-inflammatory, anti-oxidant, and immunomodulatory properties of capsaicin have been reported [1,2]. Additionally, capsaicin was found to be beneficial in the treatment of obesity, neurogenic bladder, dermatological disorders, and cardiovascular conditions [3] and in humans with different gastrointestinal conditions requiring NSAID treatment [4]. It also has carcinopreventive characteristics, which target cancer cell survival and proliferation via a variety of mechanisms including its antioxidant and anti-inflammatory activities [5-7]. Gupta, et al. [8] have outlined the role of nutrients, including capsaicin in the various stages of carcinogenesis. The relationship between chronic inflammation and the development of cancer has brought the role of pro-inflammatory cytokines in cancer to the forefront. The production of pro-inflammatory cytokines IL-1β, IL-1ra, and TNFα was reduced by peripheral blood mononuclear cells cultured with HT-29 and RKO human colon cancer cells in the presence of capsaicin. Furthermore, capsaicin inhibited cancer cell proliferation in a concentration-dependent manner without impacting the

viability of immune cells [9].

According to Aggarwal, et al. [10] capsaicin exerts its immunosuppressive effect by suppressing NF-kB activation. When capsaicin was incubated with mouse peritoneal macrophages, similar results were obtained, which were explained by restraint of NF-kB microtubule-associated protein kinase pathways [11]. Clark, et al. [12] found that capsaicin may suppress the development of cancer cells by affecting oncogenes and tumor suppressor genes. Capsaicin may affect cancer cell development by its ability to bind to the TRPV1 receptor leading to buildup intracellular calcium and apoptosis [13]. Several mechanisms, including ROS generation, NF-kB and STATS activation, are involved in inducing apoptosis in a number of tumor cells, triggered by capsaicin [14]. Additional ways that capsaicin may function as a symbiotic tool for cancer management include preventing chemoresistence and decreasing radioresistence [15], as well as enhancing the beneficial effect of the conventional anti-cancer drugs [6,13,16]. Furthermore, capsaicin prevents the function of the breast cancer resistance protein (BCRP/Abcg2) which plays a significant role in cancer endurance [17]. It is noteworthy that when loaded to nanoliposomes, capsaicin's anticancer efficacy against breast (MCF7 and MDA-MB-231), pancreatic (PANC1), and human melanoma (A375) cancer cells was significantly increased [18]. A capsaicin analogue, capsazepine, exerts anti-inflammatory and anti-cancer effects against a variety of inflammatory illnesses. Capsazepine may also prevent the growth and metastasis of tumors by altering a large variety of metabolic pathways, including the STAT and JAK kinase pathways, enhanced ROS species production, and many others [19]. Overall, it appears that capsaicin may function as a valuable tool for treating few types of cancers in addition to acting as a chemopreventer [20]. On the other hand caution was forwarded using capsaicin as a carcinopreventer, particularly at higher concentration, since it may induce undesirable effects and even promote carcinogenesis [21]. The objective of this review is to assess the benefits and drawbacks of capsaicin's role in cancer development.

Capsaicin as Carcinopreventer

Oral Cancer

Since the oral mucosa is the first site where capsaicin comes in contact during chili consumption, research has been focused on the association between capsaicin and prevalence of oral carcinoma. Due to its ability to decrease malignant cell growth and enhance apoptosis, Mosqueda-Solis, et al. [7] concluded that capsaicin may operate as a chemopreventive agent in a comprehensive review on the subject. Capsaicin exerted a marked apoptotic effect on ORL-48 oral cancer cells by activation of caspase-3,-7 and-9, leading to apoptotic DNA fragmentation and G1 phase cell cycle arrest [22]. When added to SCC-4 human tongue cancer cells capsaicin reduced the amount of viable cells by arresting mitosis at the GO/G1 phase and boosted apoptosis by increasing caspase-3 and -9 activities [23]. Capsaicin was found to sensitize oral cancer cells to conventional anticancer drugs. Treatment of HSC-3 and SAS human oral squamous carcinoma cells with 200 μM capsaicin induced sensitization of the cells to rapamycin with upregulation of autophagy caused by inhibition of the glycoprotein ribophorin II localized in the rough endoplasmic reticulum [24].

Esophageal and Gastric Cancers

Due to difficulty in detection and treatment resistance, gastrointestinal cancers are renowned for their high mortality rate. Phytochemicals such as capsaicin have proven to have a remarkable potential in chemoprevention of cancers of the upper gastrointestinal tract. Acting on its own or in combination with anti-cancer medications by a variety of molecular pathways, phytochemicals can suppress cancer growth and metastasis [25]. Treatment of 81T/VGH esophagus epidermoid carcinoma cells with capsaicin resulted in lower percentage of viable cells due to G0/G1 cell cycle arrest, enhanced apoptosis, and stimulated production of tumor suppression genes p53 and p51.In addition, Cdk2 and cyclin E complex were suppressed, whereas reactive oxygen species were promoted [26]. Esophageal squamous carcinoma cells (KYSE150, KYSE510 and KYSE410) exposed to capsaicin showed inhibited glycolysis leading to a decrease in cell proliferation connected to a PTEN, a tensin homolog and subsequent PTEN-mediated HK-2 inhibition [27]. Up-regulation of claudin3 expression, a transmembrane protein that maintains cell-to-cell contact, decreased the capacity of esophageal squamous cell carcinoma to migrate and metastasize.

In gastric cancer cells, capsaicin was found to have a proliferation suppressive effect. Lo, et al. [28] reported a concentration-dependent decrease in cell viability and enhanced apoptosis in human gastric adenocarcinoma cells (AGS) after adding capsaicin at concentrations ranging from 20μmol/L to 1mol/L over 24 hours. The maximum concentration resulted in a greater number of DNA fragments. The anti-apoptotic protein Bcl-2 expression was also dose-dependently reduced, with the maximum dose approaching zero. When it was removed from AGS cells, treatment with capsaicin drastically reduced apoptosis indicating the important role of TRPV6 as an active apoptosis mediator. Similarly, when AGS cells lacking P53 were exposed to capsaicin, apoptosis was reduced relative to P53-positive cancer cells [29].

Furthermore, activation of p53 and Bax caused increased

mitochondrial permeability [30]. Treatment of AGS cells with capsaicin induced cancer cells' apoptosis and proliferation not only by reduced Bcl-2 expression but also by caspase-3 increase and inhibited activity of phosphorylated ERK ½ and p38 Mark, two important proteins transferring signals from cell membrane receptors to the nuclear DNA, both of them acting in a dose related matter [31]. The ability of gastric cancer cells to proliferate is linked to overexpression of tNOX, according to Wang, et al. [32]. Treatment with capsaicin caused inhibition of tNOX activity resulting in a decrease in cell proliferation and a rise in apoptosis [33]. The link between capsaicin and tNOX expression was further demonstrated when it was applied on SNU-1 and TMC-1 gastric cancer cells that differed by their tNOX sensitivity to capsaicin. SNU-1 cells sensitive to capsaicin showed tNOX down-regulation with pronounced cytotoxicity and apoptosis and inhibited cell growth. On the other hand, TMC-1 cells with tNOX almost insensitive to capsaicin revealed low cytotoxicity and minimal apoptosis. tNOX-knockdown TMC-1 cells restored their sensitivity to capsaicin demonstrating the relevance of tNOX in capsaicin response [34]. Targeting TGF-β with capsaicin was found to be a useful strategy for inhibiting gastric cancer cells metastatic activity. However, this potential is dependent on SMADA4, a signal transduction protein, as it has been shown in SMADA4 deprived AGS cells which did not respond to capsaicin [35]. When coupled with cisplatin, capsaicin displayed a synergistic apoptotic capability on SNU-6768 gastric cancer cells, compared to the effect of either component alone. While combination of capsaicin and cisplatin arrested the call cycle in the G1/S phase, cisplatin affected mitosis in the G2/M. The authors discovered that cisplatin increased the promoting cytokinesis Aurora A kinase protein leading to resistance to the drug. Addition of capsaicin resulted in Aurora A degradation and increased apoptosis of cancer cells [36]. The cytotoxic effect of 5-flourouracil on HGC-27 gastric cancer cells was significantly increased when capsaicin wad added [37].

Colon Cancers

Capsaicin has been shown to have a substantial anti-proliferative effect in both animal and human colon cancer cell lines. Yoshitani, et al. [38] fed F344 rats with azoxymethane induced colon carcinogenesis with capsaicin for four weeks and observed a significant reduction of the colon carcinoma. Human colon cancer colo 205 cells treated with capsaicin showed marked apoptosis due to a drop of the anti-apoptotic Bcl-2 and increase of the pro-apoptotic Bax proteins, as well as activation of caspases -8, -9 and -3 [39]. Capsaicin enhanced nitric oxide generation, stimulated p53, Bax, caspase 3 and 9 expression, and decreased Mdm2 activity, a protein that is a negative regulator of p53 in HCT116 human colon cancer cells [40]. When Colo320DM and LoVo human colon cancer cells were exposed to capsaicin, a similar mechanism, namely significantly activated caspase-3 and enhanced ROS production, was observed [41]. Capsaicin stimulated P53 activity in human cancer cells resulting in cell cycle arrest at the GO/G1 phase and apoptosis. The importance of p53 in the process was demonstrated when the effect of capsaicin was investigated on p53 knockdown carcinoma cells [42]. Activation of AMPK, an enzyme essential for cancer development, is another way by which capsaicin induced apoptosis in HT-29 human colon carcinoma cells [43]. Capsaicin was sown to trigger apoptosis in HT-29 colon carcinoma cells in relation with PPAR gamma receptor. The capsaicin apoptotic ability was almost completely effaced when PPAR gamma activity was blocked [44]. When compared to cytotoxic nutrients like allyl isothiocyanate, β-carotene, caffeine, and lupanine (the principal alkaloid from the seeds of Lupinus exaltatus), capsaicin demonstrated the most cytotoxicity against HCT 116 p53 human colon cancer cells, with an IC50 (half maximal inhibitory concentration) value of 19.67 ± 0.06 μM [45].

Colorectal Cancers

The carcinopreventive effect of capsaicin was repeatedly observed when administered to colorectal cancer cells. Apoptosis was triggered in colorectal cancer cells by capsaicin in a variety of ways, similar to its effect on tumors of the upper gastrointestinal tract. Based on the observations that colorectal cancer cells express a low TRPV1, known as capsaicin receptor, Hou, et al. [46] have revealed that capsaicin activated TRPV1 and inhibited colorectal cell growth. Furthermore, activating P53 by capsaicin resulted in an increase in malignant cell apoptosis. Reduced geno-and cytotoxicity, as well as endorsed apoptosis and lowered cell proliferation were observed in rats bearing DMH induced colorectal carcinogenesis treated with capsaicin [47]. In comparison to normal cells, colorectal Caco-2 and OE19 cancer cells treated with capsaicin displayed enhanced cytotoxicity and apoptosis, which was explained by increased radical scavenging activity [48]. Capsaicin activated NAG1, a pro-apoptotic and growth suppressor mediator that acts synergistically with ATF3 to cause apoptosis in HCT-116, SW480, HT-29, and LoVo human colon cancer cells [49]. Suppressing the activity of β-catenin, a protein that regulates cell to cell adhesion and altering its interaction with the transcription factor TCF, capsaicin enhanced the apoptosis of the same colorectal carcinoma cells [50]. Synergistic delivery of capsaicin with other phytochemicals or substances derived from vegetables may increase its potential to induce apoptosis in colorectal cancer cells. Consequently, simultaneous treatment of colorectal cancer cells with capsaicin and 3,3'-diindolmethane isolated from Brassica plants decreased malignant cell proliferation and promoted apoptosis by altering the activity of genes like P53 and NF-kB

signaling pathways [12].

Pancreatic Cancer

Pancreatic cancer is well known for its chemoresistance and high mortality. Studies in vitro and in animal models showed that capsaicin decreased pancreatic cancer proliferation and increased apoptosis by inhibition of ROS generation that was 4-6 fold greater compared to normal cells [51]. Inhibition of β-catenin signaling by capsaicin was shown to be an additional mechanism for increased apoptosis in pancreatic cancer cells [52,53]. Exposure of AsPC-1 and BxPC-3 cells to capsaicin resulted in a dose dependent inhibition of cell viability and increase in apoptosis due to increased ROS generation and Bax expression. Oral administration of capsaicin to mice with AsPC-1 pancreatic tumor xenografts significantly slowed the growth of the tumor, while having no negative effects on normal cells [54]. Similar results were observed both in vitro and in vivo with PANC-1 and SW1990 pancreatic carcinoma bearing mice in which the inhibition of tumor cell growth proceeded through mitotic arrest in the GO/G1 phase and apoptosis with a marked expression of endoplasmic reticulum stress [55]. Apoptosis and GO/G1 arrest of PANC-1 cells in vitro and in PANC-1 xenograft mice under the influence of capsaicin has been reported by others and explained by downregulation of phpspho-PI3, p85 and phosphor-Akt kinases [56]. Notable, capsaicin in combination with other phytochemicals showed marked synergistic activity with gemcitabine in suppression of tumor growth in a preclinical model permitting a reduction of the chemotherapeutic agent [57].

Hepatocellular Carcinoma

The high mortality of hepatocellular carcinoma and its resistance to chemotherapy prompted researchers to adopt chemopreventive agents such as capsaicin, in order to increase patients' survival [58]. Similar to other malignancies, the primary mechanism by which capsaicin may result in reduced malignant cell proliferation is activation of apoptosis. Capsaicin triggered apoptosis in SK-Hep-1 hepatocellular carcinoma cells through activation of caspase-3, a mechanism that reduced Bcl-2's anti-apoptotic function and increased the pro-apoptotic Bax proteins [59]. In response to capsaicin, human hepatoma HepG2 cells produced more ROS, increased intracellular Ca2+, and enhanced apoptosis, while decreasing the expression of Bcl-2 [60]. In addition to increased ROS generation and Bcl-2 regulation, HepG2 cells treated with capsaicin showed inhibited autophagy with a consequent apoptosis stimulation [61]. Studies conducted in vivo using a rat model revealed that capsaicin restrains hepatocarcinogenesis by inhibiting the stemness malignant progenitor hepatic cells, without affecting apoptosis in normal hepatic progenitor cells. This effect was attributed to downregulation of the SIRT1/SOX2 pathway, which is active in undifferentiated stem cells [62]. HepG2 hepatocellular carcinoma cells and HL-7702 normal hepatocytes treated with capsaicin demonstrated that cancerous cells were more impacted and expressed more pronounced DNA damage and apoptosis compared to normal hepatocytes due to activation of both SIRT1 and NOX4 signaling pathways, the latter of which is a crucial constitutive in ROS generation [63]. Capsaicin exhibits a good interaction with other chemotherapeutic drugs, such as sorafenib, a drug with a beneficial effect in the course of hepatocellular carcinoma [64]. When applied together, capsaicin and sorafenib had a stronger inhibitory impact on the growth and activation of apoptosis in HepG2 and Huh-7 hepatocellular carcinoma cells than either one alone [65].

According to the authors, by causing AMPK activation, capsaicin makes cancer cells more sensitive to sorafenib. Through an enhanced phosphorylation of ERK, Zhang, et al. [66] reported similar observations of the capsaicin and sorafenib synergistic effect on cell proliferation in the same kind of cancer cells, as well as in vivo in mice with PLC/PRF/5 carcinoma xenografts. Due to enhanced caspase-3, Bax, and ADP polymerase activity, which are involved in programed cell death and apoptosis, the combined effect of capsaicin and sorafenib on LM3 cells apoptosis was noticeably stronger, whilst Bcl-2 was reduced. Additionally, cell growth and progress of metastasis was decreased [67]. The overall impression of the reports suggests that further efforts should be made into developing capsaicin as an anti-cancer medicine for treatment of gastrointestinal malignancies.

Lung Cancer

The principal risk factors for lung cancer development are smoking and environmental impacts. The high mortality rate associated with this cancer may be attributed to the inhalation of many alkaloids and polycyclic aromatic carbons in cigarette smoke. Reports reveal that capsaicin can be useful in preventing lung cancer tumorigenesis. Mice bearing lung cancer induced by benzo (a) pyrene, a polycyclic aromatic hydrocarbon, displayed a marked increase of the oxidative stress which was significantly reduced following orally treatment with capsaicin [68]. In another study the authors observed that capsaicin returned the tumor markers in the affected mice almost to normal with significant restoration of a series of cellular enzymes and signal pathways [69]. The apoptotic activity of capsaicin on human small cell lung cancer cells was found to proceed through the TRVP group. Interestingly, although TRVP1 is a capsaicin agonist, the apoptotic effect of the alkaloid needs the presence of TRVP6 receptor which is a calcium-selective TRP channel highly expressed in cells of small cell lung cancer patients, but almost completely lacking in normal epithelial cells [70].

Another mechanism by which capsaicin may inhibit the proliferation of cells from small cell lung cancer lines is by blocking the E2F transcription factors, which are important for completion of the G1/S phase of the mitotic cycle [71].

In non-small cell lung carcinoma cells capsaicin has been demonstrated to reduce cell survival by targeting P53 antigen which controls the function of mirRNA in gene expression [72] and restrains angiogenesis by activating p53-SMAR1, a tumor suppressor binding protein [73]. In mice bearing lung cancer caused by benzo (a) pyrene, capsaicin was able to mitigate the altered lipid metabolism [74]. In chickens with small cell lung xenografts and in vitro on lung cancer cells, Friedman, et al. [16] showed that capsaicin increases the apoptotic capability of camtothecin, a drug prescribed against small cell lung and other cancers.

Breast Cancer

Breast cancer is known for its high morbidity and mortality and research initiatives have been started to enhance the therapeutic outcome. Studies in vitro have demonstrated that capsaicin have the ability to cause apoptosis in breast cancer cells via a variety of ways. In H-ras transformed MCF10A human breast epithelial cells capsaicin increased ROS generation, which in turn lowered Rac-1 expression, a motility and growth regulating protein, causing apoptosis and inhibiting cell development [75]. On the other hand capsaicin triggered apoptosis in breast cancer MCF-7 cells through a caspase- independent pathway, while ROS generation was slightly reduced [30]. Thoennissen, et al. [76] reported that capsaicin decreased cell proliferation in ER (estrogen receptor)-positive and ER-negative breast cancer cell lines by interrupting the mitotic cycle at the GO/G1 phase. The expression of the epidermal growth factor receptors EGFR and HER-2 which is amplified in breast and other tumors was downregulated, while caspase activity was increased. After administering capsaicin, immunodeficient mice bearing MDA-MB231 breast cancer tumors showed a 50% reduction in tumor size without any undesirable side effects. A substantial reduction in the mitochondrial membrane potential and caspase-7 expression in the breast cancer cell lines MCF-7 and BT-20 led to an increase in apoptosis and cell death. The function of PARP1, an enzyme necessary for DNA repair, was also altered [77]. Down-regulation of the crucial oncogenic factor FBI-1, and the transcription factor NF-kB induced by capsaicin caused inhibition of MCF-7 and MDA-MB-231 breast cancer cells' proliferation and pronounced apoptosis [78].

In highly aggressive triple negative SUM149PT breast cancer cells, capsaicin stimulation of TRPV1 resulted in growth inhibition, cell destruction, and apoptosis [79]. Capsaicin efficiently suppressed cell viability, blocked the mitotic cycle at the G2/M phase, inhibited CDK8, and phosphorylation of PI3K-3 and Akt (Phosphoinositide 3-kinase, and protein kinase B, respectively) in MDA MB 231 breast carcinoma cells [80]. The preventive impact of capsaicin on breast carcinogenesis was depicted in rats with N-nitrosomethylurea-induced mammary carcinoma as marked carcinoma layers desquamation, restoration of sexual hormones, and antioxidants [81].

Prostate Cancer

Attempts have been undertaken to utilize capsaicin for the prevention and treatment of prostate cancer, which is known for having a high death rate [82]. Capsaicin targets prostate cancer cells by several ways, one of them being induction of apoptosis and inhibited cell proliferation, in both androgen receptor positive (LNCaP) and negative (PC-3 and DU-145) prostate cancer cells [82-84]. According to the authors, this action was linked to the activation of p53, p21, and Bax, as well as the downregulation of prostate specific antigen and androgen receptors. Furthermore, feeding PC-3 xenograft mice with capsaicin resulted in smaller tumors, both in terms of weight and size. LNCaP and PC-3 cells treated with capsaicin exhibited enhanced autophagy over a time and concentration-dependent manner, as well as increased production of ROS and the autophagy marker LC3-II protein [85]. According to their androgen receptors prostate carcinoma cells exert different activity on the peripheral blood mononuclear cells (PBMC) capacity for cytokine production and their response to capsaicin. PBMC incubated with both androgen resistant PC-3 cells and androgen dependent LNCaP cells showed a cell concentration increase of pro-inflammatory cytokine IL-6, while IL-1β and IL-10 increased generation was observed after interaction between PBMC and PC-3 cells only [86]. The increased IL-6 production in PC-3 cells treated with capsaicin was obstructed when the cells were incubated with an anti-TNFα antibody suggesting that IL-6 production could be dependent on TNFα secretion [87].

Others found that capsaicin decreased ceramide levels while increasing the viability of androgen dependent cells [88]. By activating c-Jun N-terminal kinases (JNK), extracellular signal-regulated kinases (ERK), and increasing ROS production, it has been observed that capsaicin enhances ceramide buildup and accelerates apoptosis in PC-3 cells [89]. The Wnt-2 signaling pathway, p-GSK3 (glycogen synthase kinase 3) and b-catenin were all suppressed in PC-3 and DU145 prostate cancer stem cells after treatment with capsaicin [90]. Capsaicin inhibits prostate cancer cell formation and proliferation by inactivating androgen receptors through increased expression of miR-449a, which are short RNA molecules that regulate post-transcriptional gene expression [91]. Treating LNCaP and PC3 prostate

cancer lines with capsaicin increased LKB1 expression by activating AMP activated kinase and promoted cell death [92].

According to Sanchez, et al. [93], PC-3 cells treated with capsaicin produced gene expression changes, with down-regulation of 10 genes and up-regulation of five, with GADD153/CHOP, a pivotal regulator of cellular stress response, being the most notable. Ramos-Torres, et al. [85] has shown that capsaicin may exert an anti-proliferative effect on LNCaP and PC-3 malignant cells by increasing the generation of ROS and LC3-II, an autophagy marker. The adenocarcinoma number and metastatic burden were significantly decreased in transgenic prostate cancer mice fed with capsaicin compared to controls. When used on PC3 prostatic cancer cells, capsaicin decreased their propensity to invade and migrate [94]. The anti-cancer effect of capsaicin has been shown to be enhanced when combined with other phytochemicals. PC-3 cells treated simultaneously with capsaicin and brassinin, a phytochemical derived from cruciferous vegetables, showed lower proliferative capacity compared with cells separately treated with the constituents. Their cytotoxicity, on the other hand, increased [95]. Because the phytochemicals have the ability to inhibit acetyltransferase tip60, which plays an important role in androgen receptor activity, PSA production, and cell proliferation, androgen-sensitive LNCaP cells treated with both capsaicin and sulforaphane showed decreased androgen receptor activity, PSA production, and cell proliferation [96].

Capsaicin inhibits the PI3K/Akt/mTOR pathway, a key cell cycle regulator, and promotes the phosphorylation of activated AMPK kinase to exert a symbiotic effect on LNCaP and PC-3 prostate cancer cells concurrently with traditional anticancer agents like docetaxel [97]. In vivo studies with LNCaP cells bearing mice have shown that capsaicin exerts radio-sensitizing effect on reduction of tumor growth when used concurrently with radiotherapy which was more pronounced when the treatments were used alone. It has been shown by in vitro studies using prostate cancer cells that capsaicin radio-sensitizing ability is achieved via inhibiting NFkB signaling [98]. Synthetic capsaicin analogues such as capsazepine have been found to decrease prostate cancer cell proliferation and delay tumor growth in animals with prostate tumors by restricting the expression of the transcription factor STAT3 [99].

Malignant Melanoma

Melanoma is renowned for its high lethality due to its quick growth, strong metastatic potential, and treatment-resistance of the tumor cells. Studies have shown that capsaicin may function in this form of malignancy as a carcinopreventive agent. When treated with capsaicin, B16-F10 melanoma cells displayed enhanced apoptosis, significant DNA fragmentation, and caspase-3 activation; this effect is thought to be mediated by Bcl-2 downregulation [100]. Cell migration was also reduced by inhibition of the PI3-K/Akt/Rac1 pathway that functions as a regulator of cell development and migration [101]. Another way by which capsaicin promotes apoptosis and interferes with the development of melanoma cells is activation of P53, a tumor suppressor antigen by TRPV1 overexpression [102]. Melanoma cell proliferation was inhibited both in vitro and in vivo when cellular tNOX and SIRT1 were inhibited by capsaicin and also led to ROS-dependent autophagy [103]. In A-375 human melanoma cells capsaicin induced apoptosis by an increase in nitric oxide and p53 production followed by caspase 3 and 9 activation [104], NADH oxidase inhibition [105] and PARP suppression [106]. Activation of NF-kappB by capsaicin was shown to inhibit melanoma cell growth by suppression of IL1-β and TNFα, both of them being upregulated in melanoma cells [107] and by increasing VEGF production which is IL1-β and TNFα independent [108].

The Other Side of the Coin

Despite the fact that studies in vitro and in experimental in vivo models are quite compelling that capsaicin may operate as a chemopreventer in a significant number of cancers, reports contend that the phytochemical has no effect on carcinogenesis, at least in certain types of malignancy [109], or even that it may accelerate the development of cancer [21,110]. The relationship between spicy food intake and the development of cancer warrants research because capsaicin is the primary phytochemical in spicy food and chili peppers. It was found that ethnic groups that consume food with high capsaicin content are at great risk for gastric cancer [111]. Researchers in Mexico City reported that people who consume chili peppers had a higher chance of developing gastric cancer than people who do not [112]. Consuming chili peppers 2-4 times per week did not enhance the incidence of colorectal cancer in a matched case-control study [113].

However, a meta-analysis based on 39 studies found a possible link between eating foods with a lot of spices and gastric cancer [114]. Another meta-analysis with 16 studies conducted by Luo, came to similar conclusions [115]. In rats with DMH-induced colon cancer given low doses (5 mg/body weight) and high doses (50 mg/body weight) of capsaicin, Caetano, et al. [116] found no differences in malignant cell proliferation and cancer development. Similar results were obtained when rats with colon and duodenal tumors caused by azoxymethane were administered 100 and 200 mg/kg of chili powder [117]. On the other hand, animals fed with red chilli (capsaicin) displayed appearance of polyps and dysplasia [118] and even tumors in the colon [119]. Thirty

six percent of 6 weeks old mice fed with capsaicin for a life-long period developed cecal tumors compared to eight percent in the controls [120]. While treatment of MGC-803 gastric cancer cells and SW-480 colon cancer cells with 16g/ml. of capsaicin reduced cell viability by roughly 40%, this effect was also seen in 80% of non-cancerous gastric mucosa GES-2 cells, indicating that capsaicin could be harmful to normal viable cells [121]. Another mechanism by which the capsaicin's carcinopreventive effect is attenuated is impaired cytotoxicity of NK cells with suppressed production of INFγ and TNFα [122].

Dose Dependence

The effect of capsaicin on cancerogenesis appears to be dose-dependent [123]. In a meta-analysis Pabalan, et al. [124] found that the positive effects of lower doses of capsaicin are distinct from those of higher doses. Low doses of capsaicin enhanced HCT116 human colon carcinoma cell proliferation and migration due to tNOX up-regulation. Suppressing tNOX activity reversed the capsaicin effect [125]. Through the activation of ROS, 12.5 μM of capsaicin treatment of HCT116 colorectal cells increased their ability to invade and migrate, while 25μM had an anti-proliferative effect [126]. Notably, comparable findings were seen in Swiss albino mice fed for 35 days which with low doses of capsaicin ranging from 0.0625% to 0.5% developed duodenal adenocarcinoma, while no tumors were seen in animals receiving the higher concentration of 1 percent [127]. Feeding mice with a lifelong diet containing 0.03125% of capsaicin caused benign polypoid adenomas in 22% of females and 14% of males, while the incidence of adenomas in the controls was 8% for both genders [120]. Mice treated for 32 days with intraperitoneal administered capsaicin at doses of 1.46 and 1.94 mg/kg showed genotoxic effects only with higher dose [128]. Following treatment with 16 μg/ml of capsaicin, the viability of SW-480 colon cancer and MGC-803 gastric cancer cells was reduced by 40%, while the toxicity with the same dose reached 80% in non-cancerous GES-1 gastric mucosal cells [129]. Capsaicin induced apoptosis in androgen-resistant prostate cells by increased production of ceramide, a pro-apoptotic factor, whereas androgen dependent cells responded to the apoptotic effect of capsaicin in a dose-dependent manner, with low doses promoting cell growth and doses over 200 μM causing apoptosis [130]. The mode of chili preparation plays a role in carcinogenesis. 100 mg/day of salted and sundried chili given to mice for 12 months caused abdominal adenocarcinoma in 35% of the animals [131].

Conclusion

Although in the majority of reports capsaicin exerted anticancer activities, its role in preventing or inducing cancer is not yet solved and attention is needed when it is intended to be used [132]. The general perception is that capsaicin's ability to either prevent cancer or encourage its growth depends on its concentration, how long it has been used, the sort of tumors it effects, and when it is consumed with food-the presence of other toxic substances [53,133]. The observation that capsaicin may affect cancer calls without damaging normal cells is of great value in cancer chemoprevention [134]. Based on the present survey and the findings in animal models it is essential to increase the efforts to investigate the anticancer potential of capsaicin in humans and to detect the appropriate administration dosage in order to add it in the list of the anti-cancer drugs.

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