Clinical and Experimental Health Sciences

The Relationship Between Capsaicin in Chili Pepper and Cancer: A Comprehensive Insight

Nevin Şanlıer, Esra Irmak, Zeynep Bengisu Ejder

Ankara Medipol University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Ankara, Türkiye.

Correspondence Author: Nevin Şanlıer
E-mail: nevintekgul@gmail.com
Received: 14.12.2022 **Accepted:** 11.01.2024

ABSTRACT

Capsicum plant consists of savage and tame types, and there is a substance named the capsaicin that causes burning sensation of the bitter peppers. Capsaicin has many effects in the body. In addition to its antioxidant and anti-inflammatory properties, it has benefits such as cancer prevention, reducing blood pressure, having analgesic effects in the body. There are different capsaicinoids such as dihydrocapsaicin, nordroydrocapsaicin, homocapsaicin in nature. These capsaicinoids provide anti-cancer activities by interacting with key signal molecules. Capsaicin can suppress the growth of cancer cells by changing the expression of the relevant genes of cancer cells. In summary, the capsaicin ensures anticancer activity by suppressing the proliferation, growth in cancer cells and to induce apoptosis which inhibit the metastasis. This situation can provide promising new treatment approaches in common and fatal cancer species today. This article revises the relationship between capsaicin and different types of cancer, anti cancer effect of capsaicin. Therewithal, studies examining the treatment of different cancer cells with various doses of capsaicin are included. Capsaicin can suppress the growth of cancer cells by changing the expression of the relevant genes of cancer cells.

Keywords: Capsaicin, cancer, TRPV1, anti-cancer, chili pepper.

1. INTRODUCTION

Red and hot peppers contain a bioactive phytochemical called capsaicin (CAP). It (8-methyl-*N*-vanillyl-6-nonenamide) is the basic content of the bitter peppers in the *Capsicum* plant genus, and it is mainly in membrane and essence of red peppers with red chilli. The domesticated species of the genus *Capsicum*, of which there are about 25 wild species, are *C. pubescens, C. chinense, C. annuum, C. frutescens and C. baccatum. C. Chinense* is the acridest type among the species (1,2). In addition to capsaicin, there are different capsaicinoids in nature, including dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin, which can cause a burning sensation when consumed (3,4). Dihydrocapsaicin and capsaicin are present in mature *Capsicum* at 1:1 and 2:1 (1,5).

Pepper has rich antioxidant features; it contains provitamin A, vitamins C and E, and carotenoids. It has been described that capsaicin has antioxidant and anti-inflammatory qualities, which have a role in lowering blood pressure, supporting weight loss, relieving pain, and preventing cancer (6). In fact, the most widely used therapeutic property of capsicum is its analgesic activity. For this reason, capsaicin is used topically as an analgesic in treating inflammation and pain in various diseases (7). It is known that transient receptor potential vanilloid type-1 (TRPV1) channels are associated with the sense of pain and are important in stimulating sensory neurons responsible for transmitting and determining pain. The active components of chili pepper stimulate TRPV1 receptors, and excessive exposure to these components causes channel desensitisation (8). TRPV1 is from the transient receptor family of cation channel receptors and mediates the analgesic effect. As a result, desensitization of sensory neurons that might cause analgesic effects and depletion of substance P are triggered by the binding of TRPV1 to capsaicin. This has also facilitated the synthesis and isolation of capsaicin-like compounds (TRPV1 agonists) with stronger analgesic effects than capsaicin (9). It has been attempted to show anti-cancer activity within human cancer, mouse models and cell culture. Synthetic and natural TRPV1 agonists could show growth inhibitory effects similar to capsaicin, and it is stated that capsaicin and its analogs show exactly independent anti-cancer activity from the TRPV1 receptor. Synthetic capsaicin mimics and natural capsaicinoids are TRPV1 ligands, but their anti-cancer activities do not include the TRPV1 receptor (6). It is shown that cancer-related pain was less experienced in TRPV1 gene suppressed rats than in the control group, which indicates that TRPV1 channels are associated with pain (10).

DOI: 10.33808/clinexphealthsci.1218885

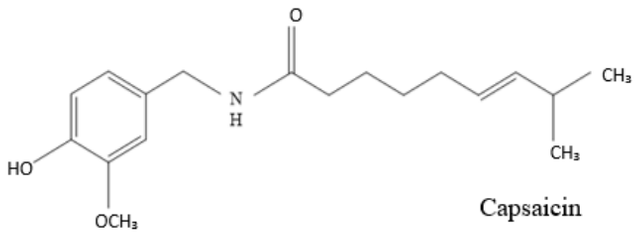

Figure 1. *The structure of capsaicin, whose anti-cancer activity was investigated in cell and animal models.*

It is estimated that 19.3 million cancer cases worldwide in 2020 will reach 28.4 million, with an increase of 47% in 2040 (11,12). The realization of anti-cancer activity is interceded by the interactivity of capsaicinoids with the key signaling molecules of the metabolic, mitochondrial and cytoplasmic survival pathways (1,7,9,13). Although capsaicin and its cellular pathways relating the anti-cancer mechanism are not clearly understood, increased intracellular calcium, suppression of mitochondrial respiration, induction of calpain activity, formation of reactive oxygen species (ROS), inhibition of coenzyme Q, multiple mechanisms included inhibition of transcription factors such as nuclear factor-kB, STAT 3 (signal transducer and transcription activator) and p53 (tumor protein 53) are included in the relevant processes (9,13-15). While the growth of human cancer cells is suppressed by capsaicin, the apoptic activity of cancer chemotherapy agents is supported by multiple mechanisms (9,13,16,17). The p-glycoprotein efflux transporters are inhibited by capsaicin in KB-C2 human endocervical adenocarcinoma cells, and the sensitization of cells to apoptosis and an increase in vinblastine concentration in the cellular microenvironment occurs as a result of treatment of KB-C2 cells with an antimicrotubule drug in the presence of capsaicin (18).

The improving of capsaicin, which is thought to be clinically beneficial for cancer treatment or pain relief, can be prevented by its side effects (9,19). Naturally, such information leads to the pursuit for capsaicin-like compounds that exhibit more anti-cancer activity than capsaicin, which has a fewer side-effect profile. Obtaining compounds with enhanced biological half-life, pharmacological activity, bioavailability, specific therapeutic index relative to capsaicin constitutes another method for the notion of capsaicin-based drug candidates (9).

Related literature review was carried out from March 2020-June 2021 through the selected websites, including World Health Organization (WHO), PubMed, Cochrane Central, Science Direct, Google Scholar, The MEDLINE, Web of Science, Embase, and www.ClinicalTrials.gov. The articles were searched using the keywords such as “capsaicin, capsaicin and its analogs, capsaicin health benefits/effects, apoptotic mechanisms in cancer cells, cancer and capsaicin, capsaicin-cancer chemoprevention mechanisms, cancer – TRPV1 – active ingredient, cancer types and apoptosis capsaicin, cancer therapies and capsaicin, proliferation in cancer”. Studies on cancer and capsaicin have investigated animal, clinical human, *in vivo* and *in vitro* studies.

2. ACTIVE COMPONENTS, MECHANISMS AND ANTI-CANCER EFFECT OF RED PEPPER

Capsaicin, the active ingredient of peppers, is said to have significant antimutagenic and anticarcinogenic activities, and capsaicin has an inhibitive effect on tumor growth in many malignant cell lines. Indeed, it can repress the growth of various cancer cells by stimulating apoptosis in many malign cell lines (20).

When the nutrient content of 100 g of edible red pepper is evaluated, and it is observed that it contains 8.81 g carbohydrates; 1.87 g of protein; 88 g of water; 1.5 g of pulp; 534 µg of beta carotene; 1.24 mg of niacin; 144 mg of ascorbic acid; 43 mg phosphorus (21). Capsaicin, a bioactive phytochemical ample in red and hot peppers, has been observed to change the expression of some genes related to cancer cell survival, metastasis, angiogenesis and growth arrest (13). Furthermore, it has been noted that capsaicin has anti-cancer properties in various cancer models (22).

Inhibition of the activity of TRPV1 channel, which is widely scattered in several non-neuronal tissues and the brain, is associated with the mechanism of action of capsaicin, becomes an anti-cancer agent in many different cancer types (7). Tumor progression is inhibited by capsaicin via suppressing angiogenesis. Capsaicin disrupts the biology of cancer stem cells, alerts non-apoptotic cell death pathways in cancer cells, kills cancer cells resistant to pro-apoptotic stimuli and is bioselective (23). Intraperitoneal implementation of capsaicin has been detected to reduce lipid peroxidation and contribute to the antitumor effect against capsaicin BP-induced lung tumorigenesis in the lungs of Swiss albino mice (15,24). It has been proclaimed that pretreatment of myoblasts with capsaicin significantly inhibits NF-jB and can alleviate LPS-induced inflammation. In contrast, small concentration of capsaicin treatment relieves systematic inflammatory cytokines during different stages of sepsis in rats (25,26). Capsaicin inhibits the proliferation of *Helicobacter pylori (H. pylori)* stimulated human gastric cancer (AGS) cells, which is manifested by decreased TNF-alpha expression and reduced infiltration of mononuclear cells into the gastric corpus and antrum (27).

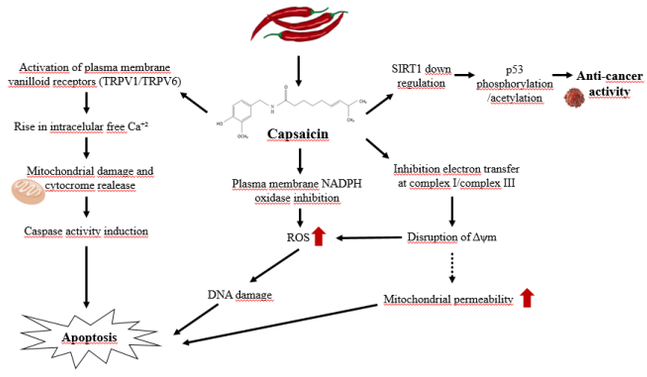

Figure 2. *Apoptosis mechanism and anticancer activity of capsaicin (28, 34)*

Arguably, identifying molecular targets involved in tumor development steps will ensure a promising strategy to fight cancer (13). Apoptosis is when cells generally destroy themselves, regulated by genes, programmed, requiring RNA, protein synthesis and energy, and maintaining homeostasis in the organism (30). Capsaicin, an alkaloid derived from peppers, has conflicting effects in both experimental and human carcinogenesis. Proposed anti-cancer mechanisms of capsaicin stimulate an increase in cell cycle arrest and apoptosis, howbeit the precise cellular mechanisms are still poorly understood (31). Nevertheless, capsaicin has been shown to target a few proteins involved in the mitochondrial death pathway in order to promote apoptosis in various cancer cell lines (13). CAP, a member of the vanilloid family, is the main component of peppers. It has been widely studied for its various pharmacological effects and impact on cell physiology, such as apoptosis and axonal growth of tumor cells is vital. It plays an important role in determining the proliferation of stem cells, in particular by modulating various signaling pathways such as CAP, C/EBPα, PPARγ and Notch signaling (32). Capsaicin shows antioxidant and antiproliferative activities. It can stimulate DNA fragmentation by apoptosis in human esophageal adenocarcinoma (OE19) and human colon adenocarcinoma (Caco-2) cell lines. Addedly, the evaluation of the selectivity index of capsaicin, defined by testing the antiproliferative activity of capsaicin in human fibroblasts, confirms the higher cytotoxicity of this spicy molecule against cancer cells within humans compared to the other cells. To examine the differences in the mechanism of action of capsaicin between cancer cells and other cells in humans, the emphasis must be placed on evaluating the different expression levels of TRPV (transient receptor potential vanilloid) receptors. These receptors play a vital role in apoptic death, determining the increase in intracellular Ca^{+2} (33). Among the proposed capsaicin anti-cancer mechanisms are cell cycle arrest and increased apoptosis (13, 34). Capsaicin can act as a carcinogen or co-carcinogen (35). It has been pinpointed that capsaicin has chemosensitizing effect and anti-cancer activity in many different human cancer types. It has been found that capsaicin compresses progression and tumorigenesis by specifically linking to the transient receptor potential TRPV1 to encourage a transient Ca2+ influx and boost Ca2+ concentration in cancer cells, suppressing proliferation and elevation of apoptosis. Some arguments support that capsazepine as a TRPV1 antagonist cannot entirely inverse the inhibitive effects of capsaicin in cancer cells. This may point to powerful mechanisms other than the TRPV1 signaling pathway that need further investigation (36). It was determined in a study that capsaicin and tNOX (tumor associated NADH oxidase) interacted to trigger the proteasomal degradation of tNOX and inhibition of NAD^{+} dependent SIRT1 (sirtuin 1) acetylase by capsaicin. As a result, acetylation levels of p53 and c-Myc, which increased cell cycle arrest and suppressed the activation of g-cyclin/cyclin-dependent kinase complexes in cancer cells, induced (37). In a study by Sarpras et al. *C. chinense* given at low doses can show cancer chemopreventive effects, induction of apoptosis and upregulation of proapoptotic genes in both cancer cell lines and mouse bone marrow cells, higher *C. chinense* dose can be used for targeted cancer therapy (38). A tumor associated NADH oxidase (ENOX2, tNOX) is inhibited by capsaicin. Thus, stimulating apoptosis reduces cancer cell growth, and capsaicin-mediated inhibition of tNOX prolongs the cell cycle. These molecular events have not been clarified (37). Another study declared that overexpression of the tribbles-related protein 3 (TRIB3) increases capsaicin-induced apoptosis. Apoptotic cell death in cancer cells occurs by regulating TRIB3 expression by capsaicin. Along with these, protein stability and gene expression improvements have also been confirmed to have a key role in capsaicin-induced regulation of TRIB3 (39). More than half of the gradual dissipation of the mitochondrial transmembrane potential and fragmentation of the mitochondria, and subsequent defective superoxide production in mitochondrial electron transport appeared to be associated with apoptosis (1). Cyclin-dependent kinases (CDKs), CDK inhibitors and cyclins form the basis of the cell cycle. When activated, CDKs allow cells to transition from one phase to another (40). It is reported that capsaicin prevents the proliferation of 5637 bladder carcinoma cells through cycle arrest by inhibition of CDK2, CDK4 and CDK6 (1).

Capsazepine is a synthetic analogue of capsaicin (29). It has been enunciated that the TRPV1 antagonist capsazepine exhibits potent anti-tumor activity in osteosarcoma cells and human prostate cancer and shows significant anti-proliferative effects against multiple tumor types *in vitro* (29, 41). In a study, it was indicated that xenograft models in athymic mice and growth of human oral squamous cell carcinoma in cell culture were suppressed by capsazepine. It has also been propounded that the apoptotic activity of capsaicin is independent of TRPV1 (41). Endoplasmic reticulum stress, increased ROS, and subsequently increased intracellular calcium in a phospholipase C-independent pathway by inducing the apoptotic activity of capsazepine. Also, an inhibitor of JAK/STAT3 signaling in prostate cancer cells is capsazepine (42). Nonetheless, capsazepine A549 sensitizes lung cancer cells to radiation therapy (41). Capsazepine can exhibit various pharmacological effects by suppressing the Ca^{2+} flow and blocking the TRPV1 channel (43). Thereupon, although its clinical use has been hindered due to its weak pharmacokinetic properties, it can be used effectively in the prevention and treatment of inflammatory conditions and various cancers (29).

3. TYPES OF CANCER AND CAPSAICIN

Recently, capsaicin has been documented to show anti-cancer activity in a fair number of human cancer types by arresting the cell cycle, suppressing proliferation, alerting apoptosis, and preventing metastasis (1,13,36). In this context, the activity of prostate cancer stem cells via Wnt/beta-Catenin was suppressed by capsaicin. Production of ROS in colon cancer cells disrupted the mitochondrial transmembrane potential and induced apoptosis (36,44,45). Capsaicin is inclined to show preventive

activity against various cancers, including the epithelial, breast, gastric, pancreatic and colon cancers (46). These activities are thought to result from capsaicin-induced activation of ASK-1 and p53 or from NADH oxidase, EGFR-HER2 signaling, MAPKs signaling and Wnt signalling (47,48). It is also agreed that capsaicin remarkably alerted apoptosis of breast cancer *in vivo* and *in vitro* and suppresses the proliferation (36). In addition, primary effusion lymphoma (PEL) is an aggressive lymphoma often resistant to conventional chemotherapies. It is divulged that capsaicin significantly inhibits the growth of Kaposi's sarcoma-associated herpesvirus (KSHV) latent infected PEL cells by inhibiting ERK, p38 MAPK and expression HIL-6, which are known to contribute to PEL survival and growth (48).

4. GASTROINTESTINAL SYSTEM CANCERS

4.1. Esophageal Cancer

In a study using the human ESCC (esophageal squamous cell carcinoma) Eca109 cell line, it was pronounced that capsaicin used at different doses prevented the proliferation of Eca109 cells. Compared to the control groups, the protein expression of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) was significantly decreased by capsaicin, and capsaicin increased the protein expression of SIRT1 in Eca109 cells, AMPK/NF-κB p65 signaling pathway. It has been ascertained that ESCC cells can inhibit the invasion and migration of ESCC cells (49). In another study, capsaicin-induced inhibition of tumor glycolysis occurred in ESCC cells. A decrease in the expression of hexokinase-2 (HK-2) involved in tumor glycolysis was observed as a result of capsaicin treatment (50).

4.2. Gastric Cancer

Gastric cancer has risk factors such as smoking, low vegetable and high salt diet, chronic gastritis with intestinal metaplasia, EBV (Epstein-Barr virus) and *H. pylori* infection (51,52). Some cancers are associated with *H. pylori* infection, whilst others are associated with different causes viz. excessive body weight, damage to gastroesophageal reflux disease (12,53). *H. pylori* infection is accepted as the main cause of non-cardiac gastric cancer (12,54). A study determined that capsaicin is a more potent pro-apoptic agent than eugenol in the presence of p53 (55). In another study, different doses of capsaicin were treated for 48 hours in colon cancer SW-480, gastric mucosal GES-1 and gastric cancer MGC-803 cells. Cytotoxicity due to capsaicin amount was defined in all three cell lines, 16 µg/mL capsaicin eliminated 80% of all living cells, capsaicin-induced cytotoxicity was not solely witnessed in cancer cells; it inhibited proliferation in cancer cells and suppressed cell growth by shifting histone acetylation in gastric cancer cell lines (52).

4.3. Liver Cancer

Aflatoxin, chronic infection with hepatitis B and C virus, excessive alcohol intake, type 2 DM and smoking constitute the main risk factors for hepatocellular carcinoma (HSC) (12,56). In a study, one HSC cell line (PLC/PRF/5, HepG2, HuH7), normal human liver cell line (HL-7702), capsaicin and kinase inhibitor drug were used at different doses. Concomitant use of capsaicin and kinase inhibitor drug significantly induced HSC cell apoptosis and enhanced the suppression of cell proliferation. Additionally, capsaicin dose-dependently boosted the phosphorylated ERK levels in PLC/PRF/5 cells, increased kinase inhibitor sensitivity, and a synergistic suppression occurred in tumor cells (57). In another study, male Wistar rats were fed a diet containing 0.01% and 0.02% capsaicin for 3 weeks. At the end of the third week, 0.02% capsaicin taken with diet increased the antioxidant glutathione system while reducing liver CD68-positive macrophages, lipid peroxidation, serum alanine aminotransferase levels and decreased hepatocyte necrosis and hepatocarcinogen diethylnitrosamine (DEN)-induced oxidative damage. In conclusion, it has been mentioned that capsaicin may be a promising chemopreventive agent when used in the early stages of hepatocarcinogenesis (58).

4.4. Pancreatic Cancer

The incidence of pancreatic cancer is higher in men than in women, and dietary factors, i.e., smoking, diabetes, increased body fat, red and processed meat consumption, and excessive alcohol intake are known to be associated with the disease (59,60). In a study, adding a combination of capsaicin and resveratrol to radiotherapy caused ROS. Capsaicin and resveratrol were found to inhibit radiotherapy-induced DNA damage molecule answer by strongly limiting the first steps of DNA double-strand break repair, keeping cells in the cell cycle and stimulating exacerbated apoptosis (61). In pancreatic cancer cells, capsaicin was found to reduce complex-I and complex-III activity in AsPC-1 and BxPC-3 cells, causing ROS formation. It is articulated that antioxidant levels in tumor cells in capsaicin-treated mice are lower than in control, mitochondrial damage and resulting in ROS accumulation. Thusly, it was determined that capsaicin treatment decreased antioxidant levels in pancreatic cancer cells by producing ROS through mitochondria and caused mitochondrial damage and apoptosis (59,61).

4.5. Colorectal Cancer

In an *in vivo* study, oral gavage administration of 20 mg/kg body weight capsaicin for four weeks reduced intestinal polyp count and the tumor burden of APCmin/+ mice. In the subsequent *in vitro* study, it was determined that capsaicin induced the phosphorylation of cyclin D1 in threonine 286 and decreased the expression of cyclin D1 in a dose – and time-dependent manner. Henceforth, it has been annunciated that capsaicin may be a potential anti-cancer agent targeting cyclin D1 degradation and proteasome activity in colon cancer (62). In another study, the Caco-2 colon cancer cell line was used, and different doses of capsaicin were applied. It illustrated that increased capsaicin dose treatment reduced the mean AgNOR

number and TAA/NA ratio (63). After colon carcinogenesis was onset in male Wistar rats, the animals were given 5 or 50 mg/kg of capsaicin three times a week by gavage for 24 weeks. High-dose capsaicin has been recorded to reduce cell proliferation and the total number of preneoplastic abnormal crypt foci (ACF) in adjacent normal-appearing colonic crypts. It was verified that capsaicin had no effect on total tumor incidence, diversity, cell proliferation, volume and apoptosis in both dose interventions (31).

5. UROGENITAL SYSTEM CANCERS

5.1. Bladder Cancer

All mammalian cells are surrounded by a multifunctional glycan layer, the glycocalyx (64,65). Between the cells and the extracellular space is the outer glycan layer, and controls processes such as endocytosis, cell adhesion and intracellular signalling (65). The glycocalyx of cancer cells depart from the healthy cells concerning the changes in the profile of proteoglycans and glycoproteins (65-69). The ability of the glycocalyx to bind cytokines and growth factors is associated with its tumor-promoting effect (65,68-70). In a study, urothelial UROtsa, human bladder cancer cell line T24, metastatic melanoma cell lines, MV3 and BLM cells were used and Ki-NCs have loaded with model lipophilic cytotoxic drug capsaicin. High-dose capsaicin ingestion has been noted to be lethal for T24 and UROtsa cells (65). In another study, the T24 bladder cancer cell line was used. The effect on the 24-hour cell migration rate was investigated using different doses of capseisin (control, 10, 100 and 200 µM). The usage of 100 and 200 µM capseicin was effective in cell migration in T24 cells, and SIRT1 expression was found to be decreased in T24 bladder cancer cells (71).

5.2. Prostate Cancer

It has been communicated that capsaicin has anti-tumor properties against prostate cancer, inhibits the development of prostate cancer cells, and reduces prostate enlargement in animal models (72,73). At the same time, capsaicin can initiate apoptosis in human prostate carcinoma cells by causing cell cycle arrest (73). It was observed that capsaicin alerted prostate cell death with time and dose difference and rised the amount of cargo protein with LC3-II, which is an autophagy marker. Capsaicin treatment increases lysosomes localized with LC3 positive vesicles and inhibits autophagolysosome degradation. In conclusion, ROS-mediated capsaicin-induced autophagy obstruction promotes antiproliferation in prostate cancer cells (73). In another study, prostate cancer PC3 and LNCaP cell lines were used to treat capsaicin with chemotherapy. It has been uttered that there is a significant decrease in the growth of cells in the combined use of capsaicin and chemotherapy drug (74). Another study stated that the viability of human prostate cancer DU145 and PC-3 cells was decreased by capsaicin, and the Wnt/β-catenin pathway, which is the leading pathway in regulating the activity of cancer stem cells, was inactivated by capsaicin (45).

6. OTHER CANCERS

6.3. Breast Cancer

It is recommended to define and improve other efficient therapeutic agents to reduce side effects and develop the treatment efficacy of chemotherapy in breast cancer (36). In this study, capsaicin induced apoptosis while inhibiting proliferation in breast cancer cells. At the same time, capsaicin inhibits proliferation and promotes apoptosis, which is closely related to FBI-1 (for factor that binds to the inducer of short transcripts). The primary mechanism may be relatived to FBI-1-mediated down-regulation of the NF-κB pathway, and linking capsaicin and FBI-1 may provide an encouraging treatment for breast cancer patients (36).

6.4. Lung Cancer

Small cell lung cancer (SCLC) corresponds to 15-20% of lung cancer cases. It is the most aggressive type of lung cancer (75-77). In a study investigating the anti-cancer activity of the drug and capsaicin combination, it was determined that low-dose capsaicin synergized with the drug and induced apoptosis at the high levels in human SCLC cells. It was reported that human SCLC cells were sensitized to the apoptotic activity of the drug by capsaicin (77). The combined treatment of capsaicin with 5-FU in NSCLC (non-small cell lung cancer) cells and its cytotoxicity were investigated. To determine the relationship between TS expression and capsaicin, H1703 and H520 cells were given 100 µM or different doses of capsaicin for 4-24 hours. It has been reported that while capsaicin decreases protein expression and TS mRNA in a time and dose-dependent manner, it also decreases phospho-p38 MAPK expression through capsaicin (78).

6.5. Bone Cancer

The incidence varies depending on many factors such as age, gender, race (79,80). In a study, the human osteosarcoma cell line MG-63 was used. Using different doses of capsaicin and cisplatin, capsaicin and cisplatin significantly inhibited the growth of MG-63 cells in a dose-dependent manner. Capsaicin is defined as an anti-cancer agent that can induce immunological cell death in human osteosarcoma cells *in vitro* (81). In another study, OS cell lines HOS, 143B and MG63 were used, and when capsaicin was used at different doses, it caused a dose-dependent to reduce in cell viability in all 3 OS cell lines. High concentrations of capsaicin can activate caspase-dependent apoptotic signaling pathways in OS cells. Capsaicin also reduced colony formation ability in 3 OS cell lines from 100-µM dose (82). The studies evaluating the anti-cancer activity of capsaicin and capsazepine in different cancer types are shown in Table 1.

Table 1. *Studies evaluating the anti-cancer activity of capsaicin and capsazepine in different cancer types*

Cancer Types	Study Design	Intervention	Effects
Breast Cancer (83)	*In vitro* study MDA-MB-231 breast cancer cell Control group MCF10A healthy breast cells Induction with capsaicin at doses of 10, 50, 100, and 200 µM	MTT, cell scratch analysis, cell cycle analysis, cell transfection, reverse transcription-quantitative PCR, and western blotting	Viability and migration of MDA-MB-231 breast cancer cells were inhibited by capsaicin Capsaicin induced G2/m cell cycle arrest in MDA-MB-231 cells
Breast Cancer (84)	Polyethylene glycol-conjugated CAP[a] (PEG-Fmoc-CAP_2) polymeric prodrug micelle carrier designed and physically encapsulated with PTX[b] (PTX:paclitaxel)	Synergistic anti-cancer therapy with PTX and CAP	70.5% reduction in tumor growth in mice treated with PTX/CAP-loaded micelles Compared to other treatments, PTX/CAP-loaded micelle shows high *in vivo* antitumor activity in inhibiting tumor growth.
Lung Cancer (77)	Small cell lung cancer cells	Capsaicin and camptothecin at doses of 0, 0.01, 0.1, 1.0, 10.0, 100.0 µM Concomitant use of camptothecin and capsaicin	Human small cell lung cancer cells are sensitized to the apoptotic activity of camptothecin by capsaicin.
Lung Cancer (78)	Non-small cell lung cancer cells H520 and H1703 cells	Concomitant use of capsaicin and 5-FU[c] at different concentrations	Concomitant use of 5-FU and capsaicin has a synergistic cytotoxiceffect on H520 and H1703 cells.
Lung Cancer (85)	Human lung cancer cell line-H1299	Capsaicin at 100 and 200 µM doses	Capsaicin reduces mutant p53 levels and helps cancer cell destruction Reactivates wild-type p53 protein and promotes reactivated p53 cell death
Gastric Cancer (52)	SW-480, gastric cancer MGC-803 and gastric mucosa GES-1 cells	Capsaicin at doses of 0, 2, 4, 8, 16 µg/mL	Inhibited proliferation in cancer cells Suppresses cell growth by altering histone acetylation
Gastric Cancer (55)	The human stomach cell line AGS	Capsaicin in different doses (50, 100, 150, 200, 250, 300, 350 µM) Eugenol in different doses (0.1, 0.4, 0.7, 1.0, 1.4, 1.7 mM)	Capsaicin is a more potent pro-apoptic agent than eugenol.
Prostate Cancer (73)	Human prostate epithelial PC-3 and LNCaP cells	Capsaicin at 20 and 80 µM doses	Increased amount of cargo protein with autophagy marker LC3-II Capsaicin has an anti-proliferative effect on LNCaP and PC-3 prostate cells.
Prostate Cancer (74)	PC3 and LNCaP human prostate cancer cell lines	Concomitant use of Capsaicin and Docetaxel	Capsaicin and docetaxel inhibited the growth of prostate cancer cells with a synergistic effect.
Prostate Cancer (45)	Human prostate cancer PC-3 and DU145 cells	Capsaicin at doses of 1, 5, 10 µM	Dose-dependent capsaicin significantly reduced the viability of PC-3 tumors PC-3 and DU145 down-regulated the protein and mRNA expression of CD133, CD44, ALDH1A1, OCT-4, Nanog and Sox2 in cancer stem cells Capsaicin inactivated the Wnt/β-catenin pathway
Colon Cancer (62)	*In vivo* $APC^{min/+}$ mice *In vitro* Human colon cancer cells (SW480, HCT116, LoVo and Caco-2)	*In vivo* Oral gavage administration of capsaicin at a dose of 20 mg/kg body weight for 4 weeks *In vitro* Capsaicin in different doses (0, 12.5, 25, 50 µM)	*In vivo* A tendency to reduce polyp count and tumor burden in the gut of $APC^{min/+}$ mice was observed. *In vitro* Capsaicin induces phosphorylation of cyclin D1 at T286 and decreases cyclin D1 expression in a dose – and time-dependent manner.
Colon Cancer (63)	Human colon cancer Caco-2 cells	Capsaicin in different doses (25uµ, 50uµ and 75uµ)	Mean AgNOR number and TAA/NA ratio decrease with increasing capsaicin dose therapy.
Colon Cancer (31)	Male Wistar rats	Capsaicin 5 or 50 mg/kg 3 times a week by gavage for 24 weeks	High-dose capsaicin induced cell proliferation in adjacent normal-appearing colonic crypts and reduced total number of preneoplastic ACFs.

Bladder Cancer (86)	Human bladder cancer T24 cell line Second degree carcinoma, cat 5637 cells Male NOD/SCID mice	Capsaicin was given at doses of 0, 50, 100, 150, 200 and 300 µm.	Capsaicin inhibited cell proliferation and migration in bladder cancer cells Capsaicin injection suppressed tumor growth *in vivo* Induces ROS production in bladder cancer cells via the FOXO3a-mediated pathway. Triggered cell cycle arrest in G0/G1 phase
Bone Cancer (81)	Human osteosarcoma cell line MG-63	0.50, 100, 150 µg/ml doses of cisplatin and 0, 100, 200, 300, 400 and 500 µM doses of capsaicin were given.	Capsaicin and cisplatin significantly inhibited the growth of MG-63 cells in a dose-dependent manner. Capsaicin induces immunological cell death in OS[d] cells
Bone Cancer (82)	OS cell lines MG63, 143B and HOS	Capsaicin was given in doses of 50-100-150-200-250-300 µM	Decreased cell viability Inhibitory effect on cell proliferation Activation in caspase-dependent apoptotic signaling pathways
Bone Cancer (87)	Human osteosarcoma cell line MG-63	5, 10, 20, 40 µM capsaicin was given	Capsaicin induces loss of cell viability and apoptosis Capsaicin activates AMPK[e], p53 and JNK[f]. Capsaicin causes cell death by activation of TRPV1[g]-dependent and independent pathways in MG-63 cells.
Liver Cancer (57)	PLC/PRF/5, HuH7, HepG2 hepatocellular carcinoma cell lines and human liver HL-7702 cell line	Capsaicin (0.50,100,150,200,250 µM), sorafenib (0-0.3-1-3-10-30 µmol/L) were given	Suppression of cell proliferation significantly increased Suppression of tumor growth
Liver Cancer (58)	Male Wistar rats	Diet containing 0.01% and 0.02% capsaicin was given for 3 weeks	Decreased serum alanine aminotransferase levels, lipid peroxidation, liver CD68-positive macrophages Decreased oxidative damage and hepatocyte necrosis caused by hepatocarcinogen diethylnitrosamine
Liver Cancer (88)	Human hepatocellular carcinoma HepG2 cell line and human hepatoma cell line Huh-7	Capsaicin was given in doses of 10, 20, 40, 75 µM, sorafenib was given in doses of 0.2, 0.4, 1.5, 2 µM	The combination of capsaicin and sorafenib strongly inhibited growth in HepG2 and Huh-7 cells An increase in apoptosis has been observed Capsaicin alone and in combination with sorafenib induced AMPK activation and acetyl CoA carboxylase phosphorylation in HCC[h] cells.
Pancreatic cancer (61)	8 to 12 week old Swiss male mice and pancreatic cancer cell lines	When tumors reached approximately 100mm^3, mice were given resveratrol and capsaicin in combination with gavage.	Addition of resveratrol and capsaicin combination to radiotherapy increased ROS production Significantly reduced tumor volume in mice
Esophageal Cancer (49)	Human ESCC Eca109 cell line	Capsaicin was given in different doses (0, 25, 50 and 100 µM)	Inhibited proliferation in Eca109 cells Decreased expression of MMP-9 and MMP-2
Esophageal Cancer (50)	Esophageal squamous cell carcinoma (ESCC) cells	Capsaicin was treated at doses of 0, 30, 60, 120 µM.	Decreased HK-2 expression Inhibition on tumor glycolysis in ESCC[i] cells

CAP[a] = capsaicin, PTX[b] = paclitaxel, 5-FU[c] = fluorouracil, OS[d] = osteosarcoma, AMPK[e] = 5' adenosine monophosphate-activated protein kinase, JNK[f] = c-Jun N-terminal kinase, TRPV1[g] = transient receptor potential vanilloid member 1, HCC[h] = hepatocellular carcinoma, ESCC[i] = Esophageal squamous cell carcinoma, STAT3[j] = signal transducer and activator of transcription 3, OSCC[k] = oral squamous cell carcinoma

7. CONCLUSIONS

Capsaicin is a bioactive compound that has recently attracted scholarly attention with its applications in pharmacobiology against cancer. Even though different Capsicum species include high levels of capsaicin, not all of these species can be used as capsaicin sources. More studies on anti-cancer targets of capsaicin, the potential of new treatments in the future, and the possible efficacy in cancer treatment and prevention seem to be required. That said, although clinical studies are not sufficient, it is argued that data on capsaicin concentrations, ways of administration and long-term side effects should be well understood prior to use.

Acknowledgements: *Nevin Sanlıer conducted the literature research and drafted the manuscript. Nevin Sanlıer revised the draft critically. All authors contributed to this review. All authors read and approved the final manuscript.*
Funding: *The authors received no specific funding for this work.*

Conflict of interests: *The authors declare that they have no conflict of interest disclosed in this work.*
Authors Contribution:
Research idea: NS, EI, ZBE
Design of the study: NS, EI, ZBE
Drafting the manuscript: NS, EI, ZBE
Revising it critically for important intellectual content: NS, EI, ZBE
Final approval of the version to be published: NS, EI, ZBE

REFERENCES

[1] Chapa-Oliver AM, Mejía-Teniente L. Capsaicin: From plants to a cancer-suppressing agent. Molecules. 2016;21:931. DOI: 10.3390/molecules21080931

[2] Kehie M, Kumaria S, Tandon P. Manipulation of culture strategies to enhance capsaicin biosynthesis in suspension and immobilized cell cultures of Capsicum chinense Jacq. cv.

Naga King Chili. Bioprocess Biosyst Eng. 2014;37:1055-1063. DOI: 10.1007/s00449.013.1076-2

[3] Srinivasan K. Biological activities of red pepper (Capsicum annuum) and its pungent principle capsaicin: a review. Crit Rev Food Sci Nut. 2016;56:1488-1500. DOI: 10.1080/10408.398.2013.772090

[4] Lu M, Chen C, Lan Y, Xiao J, Li R, Huang J, Ho CT. Capsaicin—the major bioactive ingredient of chili peppers: Bio:efficacy and delivery systems. Food Funct. 2020;11:2848-2860. DOI: 10.1039/D0FO00351D

[5] Prasad BCN, Shrivastava R, Ravishankar GA. Capsaicin. Evid-Based-Integrative-Med. 2005;2:147-166. DOI: 10.2165/01197.065.2005020.300.0006

[6] Wang F, Xue Y, Fu L, Wang Y, He M, Zhao L, Liao X. Extraction, purification, bioactivity and pharmacological effects of capsaicin: a review. Crit Rev Food Sci Nut. 2021;1-29. DOI: 10.1080/10408.398.2021.1884840

[7] Basith S, Cui M, Hong S, Choi S. Harnessing the therapeutic potential of capsaicin and its analogues in pain and other diseases. Molecules. 2016; 21:966. DOI: 10.3390/molecules21080966

[8] Malmberg AB, Bley KR. Turning up the heat on pain: TRPV1 receptors in pain and inflammation. Springer Science & Business Media; 2005.

[9] Friedman JR, Nolan NA, Brown KC, Miles SL, Akers AT, Colclough KW, Dasgupta P. Anticancer activity of natural and synthetic capsaicin analogs. J Pharmacol Exp Ther. 2018;364:462-473. DOI: 10.1124/jpet.117.243691

[10] Ghilardi JR, Röhrich H, Lindsay TH, Sevcik MA, Schwei MJ, Kubota K, Mantyh PW. Selective blockade of the capsaicin receptor TRPV1 attenuates bone cancer pain. J Neurosci. 2005;25:3126-3131. DOI: 10.1523/JNEUROSCI.3815-04.2005

[11] Zhang S, Wang D, Huang J, Hu Y, Xu Y. Application of capsaicin as a potential new therapeutic drug in human cancers. J Clin Pharm Ther. 2020;45:16-28. DOI: 10.1111/jcpt.13039

[12] Sung H, Ferlay J, Siegel RL, Laversanne M. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-249. DOI: 10.3322/caac.21660

[13] Clark R, Lee SH. Anticancer properties of capsaicin against human cancer. Anticancer Res. 2016;36:837-843.

[14] Fernandes ES, Cerqueira ARA, Soares AG, Costa SK. Capsaicin and its role in chronic diseases. Adv Exp Med Biol. 2016;91-125. DOI: 10.1007/978-3-319-41342-6_5

[15] Cho SC, Lee H, Choi BY. An updated review on molecular mechanisms underlying the anticancer effects of capsaicin. Food Sci Biotechnol. 2017;26:1-13. DOI: 10.1007/s10068.017.0001-x

[16] Arzuman L, Beale P, Yu JQ, Huq F. Synthesis of tris (quinoline) monochloroplatinum (II) chloride and its activity alone and in combination with capsaicin and curcumin in human ovarian Cancer cell lines. Anticancer Res. 2016;36(6):2809-2818.

[17] Vendrely V, Peuchant E, Buscail E, Moranvillier I, Rousseau B, Bedel A, Brillac A, de Verneuil H, Moreau-Gaudry F, Dabernat S. Resveratrol and capsaicin used together as food complements reduce tumor growth and rescue full efficiency of low dose gemcitabine in a pancreatic cancer model. Cancer Lett. 2017;390:91-102. DOI: 10.1016/j.canlet.2017.01.002

[18] Silva R, Vilas-Boas V, Carmo H, Dinis-Oliveira RJ, Carvalho F, de Lourdes Bastos M, Remião F. Modulation of P-glycoprotein efflux pump: induction and activation as a therapeutic strategy. Pharmacol Ther. 2015;149:1-123. DOI: 10.1016/j.pharmthera.2014.11.013

[19] Evangelista S. Novel therapeutics in the field of capsaicin and pain. Expert Rev Clin Pharmacol. 2015;8(4):373-375. DOI: 10.1586/17512.433.2015.1044438

[20] Chu H, Li M, Wang X. Capsaicin induces apoptosis and autophagy in human melanoma cells. Oncol Lett. 2019;17:4827-4834. DOI: 10.3892/ol.2019.10206

[21] USDA. 2019. https://fdc.nal.usda.gov/fdc-app.html#/food-details/170106/nutrients

[22] Cao S, Chen H, Xiang S, Hong J, Weng L, Zhu H, Liu Q. Anti-cancer effects and mechanisms of capsaicin in chili peppers. AJPS. 2015;6:3075. DOI: 10.4236/ajps.2015.619300

[23] Lau JK, Brown KC, Dom AM, Witte TR, Thornhill BA, Crabtree CM, Dasgupta P. Capsaicin induces apoptosis in human small cell lung cancer via the TRPV6 receptor and the calpain pathway. Apoptosis. 2014;19:1190-1201. DOI: 10.1007/s10495.014.1007-y

[24] Anandakumar P, Kamaraj S, Jagan S, Ramakrishnan G, Vinodhkumar R, Devaki T. Capsaicin modulates pulmonary antioxidant defense system during benzo (a) pyrene-induced lung cancer in swiss albino mice. Phytother Res. 2008;22:529-533. DOI: 10.1002/ptr.2393

[25] Shang K, Amna T, Amina M, Al-Musayeib NM, Al-Deyab SS, Hwang I. Influence of capsaicin on inflammatory cytokines induced by lipopolysaccharide in myoblast cells under *in vitro* environment. Pharmacogn Mag. 2017;13:26. DOI: 10.4103/0973-1296.203984

[26] Wang J, Tian W, Wang S, Wei W, Wu D, Wang H, Li Y. Anti-inflammatory and retinal protective effects of capsaicin on ischaemia-induced injuries through the release of endogenous somatostatin. Clin Exp Pharmacol Physiol. 2017;44:803-814. DOI: 10.1111/1440-1681.12769

[27] Toyoda T, Shi L, Takasu S, Cho YM, Kiriyama Y, Nishikawa A, Tsukamoto T. Anti-inflammatory effects of capsaicin and piperine on Helicobacter pylori-induced chronic gastritis in mongolian gerbils. Helicobacter. 2016;21:131-142. DOI: 10.1111/hel.12243

[28] Hail N, Lotan R. Cancer chemoprevention and mitochondria: targeting apoptosis in transformed cells via the disruption of mitochondrial bioenergetics/redox state. Mol Nutr Food Res. 2009;53:49-67. DOI: 10.1002/mnfr.200700527

[29] Yang MH, Jung SH, Sethi G, Ahn KS. Pleiotropic pharmacological actions of capsazepine, a synthetic analogue of capsaicin, against various cancers and inflammatory diseases. Molecules 2019;24:995. DOI: 10.3390/molecules24050995

[30] Coşkun G, Özgür H. Molecular mechanism of apoptosis and necrosis. Arch Med Rev Journal. 2011;20:145-158

[31] Caetano BFR, Tablas MB, Ignoti MG, de Moura NA, Romualdo GR, Barbisan LF, Rodrigues MAM. Capsaicin lacks tumor-promoting effects during colon carcinogenesis in a rat model induced by 1, 2-dimethylhydrazine. Environ Sci Pollut Res Int. 2021;28:2457-2467. DOI: 10.1007/s11356.020.10683-6

[32] Yuan M, Zhao L, Li Y, Gao X, Zhang B, Zhang D, Li Y. Capsaicin on stem cell proliferation and fate determination-a novel perspective. Pharmacol Res. 2021;105566. DOI: 10.1016/j.phrs.2021.105566

[33] Lavorgna M, Orlo E, Nugnes R, Piscitelli C, Russo C, Isidori M. Capsaicin in hot chili peppers: *In vitro* evaluation of its antiradical, antiproliferative and apoptotic activities. Plant

Foods Hum Nutr. 2019;74:164-170. DOI: 10.1007/s11130.019.00722-0

[34] Oyagbemi AA, Saba AB, Azeez OI. Capsaicin: a novel chemopreventive molecule and its underlying molecular mechanisms of action. Indian J Cancer. 2010;47:53. DOI: 10.4103/0019-509X.58860

[35] Yang J, Li TZ, Xu GH, Luo BB, Chen YX, Zhang T. Low-concentration capsaicin promotes colorectal cancer metastasis by triggering ROS production and modulating Akt/mTOR and STAT-3 pathways. Neoplasma. 2013;60:364-372. DOI: 10.4149/neo_2013_048

[36] Chen M, Xiao C, Jiang W, Yang W, Qin Q, Tan Q, Wei C. Capsaicin inhibits proliferation and induces apoptosis in breast cancer by down-regulating FBI-1-mediated NF-κB pathway. Drug Des Devel Ther. 2021;5:125. DOI: 10.2147/DDDT.S269901

[37] Islam A, Su AJ, Zeng ZM, Chueh PJ, Lin MH. Capsaicin targets tNOX (ENOX2) to inhibit G1 Cyclin/CDK complex, as assessed by the cellular thermal shift assay (CETSA). Cells. 2019;8:1275. DOI: 10.3390/cells8101275

[38] Sarpras, M. – Chhapekar, S. S. – Ahmad, I, Abraham, S.K., Ramchiary, N. Analysis of bioactive components in Ghost chili (Capsicum chinense) for antioxidant, genotoxic, and apoptotic effects in mice. Drug Chem Toxicol. 2020;43:182–191. DOI: 10.1080/01480.545.2018.1483945

[39] Lin RJ, Wu IJ, Hong JY, Liu BH, Liang RY, Yuan TM, Chuang SM. Capsaicin-induced TRIB3 upregulation promotes apoptosis in cancer cells. Cancer Manag Res. 2018;10:4237. DOI: 10.2147/CMAR.S162383

[40] Final report on the safety assessment of capsicum annuum extract, capsicum annuum fruit extract, capsicum annuum resin, capsicum annuum fruit powder, capsicum frutescens fruit, capsicum frutescens fruit extract, capsicum frutescens resin, and capsaicin. Int J Toxicol. 2007;26(1):3-106. DOI: 10.1080%2F109.158.10601163939

[41] Nishino K, Tanamachi K, Nakanishi Y, Ide S, Kojima S, Tanuma SI, Tsukimoto M. Radiosensitizing effect of TRPV1 channel inhibitors in cancer cells. Biol Pharm Bull. 2016; b16 00080. DOI: 10.1248/bpb.b16-00080

[42] Friedman JR, Nolan NA, Miles SL, Brown KC, Akers AT, Colclough KW, Seidler JM, Rimoldi JM, Valentovic MA, Dasgupta P. Anti-cancer activity of natural and synthetic capsaicin analogs. J Pharmacol Exp Ther. 2017;364(3)

[43] Sung B, Prasad S, Ravindran J, Yadav VR, Aggarwal BB. Capsazepine, a TRPV1 antagonist, sensitizes colorectal cancer cells to apoptosis by TRAIL through ROS–JNK–CHOP-mediated upregulation of death receptors. Free Radic Biol Med. 53;2012:1977-1987. DOI: 10.1016/j.freeradbiomed.2012.08.012

[44] Yang K, Pyo J, Kim GY, Yu R, Ju S, Kim W, Kim BS. Capsaicin induces apoptosis by generating reactive oxygen species and disrupting mitochondrial transmembrane potential in human colon cancer cell lines. Cell Mol Biol Lett. 2009;4:497-510. DOI: 10.2478/s11658.009.0016-2

[45] Zhu M, Yu X, Zheng Z, Huang J, Yang X, Shi H. Capsaicin suppressed activity of prostate cancer stem cells by inhibition of Wnt/β-catenin pathway. Phytother Res. 2021;34:817-824. DOI: 10.1002/ptr.6563

[46] Richbart SD, Friedman JR, Brown KC, Gadepalli RS, Miles SL, Rimoldi JM, Dasgupta P. Nonpungent N-AVAM capsaicin analogues and cancer therapy. J Med Chem. 2021;64:1346-1361. DOI: 10.1021/acs.jmedchem.0c01679

[47] Thoennissen NH, O'kelly J, Lu D, Iwanski GB, La DT, Abbassi S, Koeffler HP. Capsaicin causes cell-cycle arrest and apoptosis in ER-positive and-negative breast cancer cells by modulating the EGFR/HER-2 pathway. Oncogene. 2010;29:285-296. DOI: 10.1038/onc.2009.335

[48] Moriguchi M, Watanabe T, Kadota A, Fujimuro M. Capsaicin induce apoptosis in KSHV-positive primary effusion lymphoma by suppressing ERK and p38 MAPK signaling and IL-6 expression. Front Oncol. 2019;9:83. DOI: 10.3389/fonc.2019.00083

[49] Guo Y, Liu N, Liu K, Gao M. Capsaicin inhibits the migration and invasion via the AMPK/NF-κB signaling pathway in esophagus sequamous cell carcinoma by decreasing matrix metalloproteinase-9 expression. Biosci Rep. 2019;39. DOI: 10.1042/BSR20190819

[50] Mao X, Zhu H, Luo D, Ye L, Yin H, Zhang J, Zhang Y. Capsaicin inhibits glycolysis in esophageal squamous cell carcinoma by regulating hexokinase-2 expression. Mol Med Rep. 2018;17:6116-6121. DOI: 10.3892/mmr.2018.8574

[51] Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Schlemper RJ. Helicobacter pylori infection and the development of gastriccancer. N Engl J Med. 2001;345:784-789. DOI: 10.1056/nejmoa001999

[52] Wang F, Zhao J, Liu D, Zhao T, Lu Z, Zhu L, Cai Y. Capsaicin reactivates hMOF in gastric cancer cells and induces cell growth inhibition. Cancer Biol Ther. 2016;17:1117-1125. DOI: 10.1080/15384.047.2016.1235654

[53] Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D. cancer epidemiology and prevention. Oxford University Press; 2017.

[54] Hooi, J. K. – Lai, W. Y. – Ng, W. K, Suen MM, Underwood FE, Tanyingoh D, Ng SC. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology. 2017;153:420-429.

[55] Sarkar A, Bhattacharjee S, Mandal DP. Induction of apoptosis by eugenol and capsaicin in human gastric cancer AGS cells-elucidating the role of p53. Asian Pac J of Cancer Prev. 2015;16:6753-6759. DOI: 10.7314/APJCP.2015.16.15

[56] Petrick JL, Yang B, Altekruse SF, Van Dyke AL, Koshiol J, Graubard BI, McGlynn K. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: A population-based study in SEER-Medicare. PloS One. 2017;12:e0186643. DOI: 10.1371/journal.pone.0186643

[57] Zhang SS, Ni YH, Zhao CR, Qiao Z, Yu HX, Wang LY, Gao JJ. Capsaicin enhances the antitumor activity of sorafenib in hepatocellular carcinoma cells and mouse xenograft tumors through increased ERK signaling. Acta Pharmacol Sin. 2018;39:438-448. DOI: 10.1038/aps.2017.156

[58] Sarmiento-Machado LM, Romualdo GR, Zapaterini JR, Tablas MB, Fernandes AAH, Moreno FS, Barbisan LF. Protective effects of dietary capsaicin on the initiation step of a two-stage hepatocarcinogenesis rat model. Nutr Cancer. 2021;73:817-828. DOI: 10.1080/01635.581.2020.1764067

[59] Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, Bray F. Global burden of 5 major types of gastrointestinal cancer. Gastroenterology. 2020;159: 335-349. DOI: 10.1053/j.gastro.2020.02.068

[60] WCRF/AICR. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. 2007.

[61] Vendrely V, Amintas S, Noel C, Moranvillier I, Lamrissi I, Rousseau B, Dabernat S. Combination treatment of resveratrol and capsaicin radiosensitizes pancreatic tumor cells by unbalancing DNA repair response to radiotherapy towards cell death. Cancer Lett. 2019;451:1-10. DOI: 10.1016/j.canlet.2019.02.038

[62] Lee SH, Clark R. Anti-tumorigenic effects of capsaicin in colon cancer. J Food Chem Nanotechnol. 2016;2:162-167. DOI: 10.17756/jfcn.2016-025

[63] Nisari M, Eröz R. Does capsaicin have therapeutic benefits in human colon adenocarcinoma? Selection of the most reliable dose via AgNOR. Turk J Med Sci. 2020;50:1076-1081. DOI: 10.3906/sag-2003-251

[64] Kang H, Wu Q, Sun A, Liu X, Fan Y, Deng X. Cancer cell glycocalyx and its significance in cancer progression. Int J Mol Sci. 2018;19:2484. DOI: 10.3390/ijms19092484

[65] von Palubitzki L, Wang Y, Hoffmann S, Vidal-y-Sy S, Zobiak B, Failla AV, Gorzelanny C. Differences of the tumour cell glycocalyx affect binding of capsaicin-loaded chitosan nanocapsules. Sci Rep. 2020;10:1-16. DOI: 10.1038/s41598.020.79882-y

[66] Paszek MJ, DuFort CC, Rossier O, Bainer R, Mouw JK, Godula K, Weaver VM. The cancer glycocalyx mechanically primes integrin-mediated growth and survival. Nature. 2014;511:319-325. DOI: 10.1038/nature13535

[67] Kuo JCH, Gandhi JG, Zia RN, Paszek MJ. Physical biology of the cancer cell glycocalyx. Nat Phys. 2018;14:658-669. DOI: 10.1038/s41567.018.0186-9

[68] Gandhi JG, Koch DL, Paszek MJ. Equilibrium modeling of the mechanics and structure of the cancer glycocalyx. Biophys. J 2019;116:694-708. DOI: 10.1016/j.bpj.2018.12.023

[69] Buffone A, Weaver VM. Don't sugarcoat it: How glycocalyx composition influences cancer progression. J Cell Biol. 2020;219(1):e201910070. DOI: 10.1083/jcb.201910070

[70] Oo HZ, Seiler R, Black PC, Daugaard M. Post-translational modifications in bladder cancer: expanding the tumor target repertoire. Urol Oncol. 2020;38:858-866. DOI: 10.1016/j.urolonc.2018.09.001

[71] Islam A, Yang YT, Wu WH, Chueh PJ, Lin MH. Capsaicin attenuates cell migration via SIRT1 targeting and inhibition to enhance cortactin and β-catenin acetylation in bladder cancer cells. Am J Cancer Res. 2019;9:1172.

[72] Venier NA, Colquhoun AJ, Sasaki H, Kiss A, Sugar L, Adomat H, Venkateswaran V. Capsaicin: a novel radio-sensitizing agent for prostatat cancer. Prostate. 2015;75:113-125. DOI: 10.1002/pros.22896

[73] Ramos-Torres Á, Bort A, Morell C, Rodríguez-Henche N, Díaz-Laviada I. The pepper's natural ingredient capsaicin induces autophagy blockage in prostatat cancer cells. Oncotarget. 2016;7:1569. DOI: 10.18632/oncotarget.6415

[74] Sánchez BG, Bort A, Mateos-Gómez PA, Rodríguez-Henche N, Díaz-Laviada I. Combination of the natural product capsaicin and docetaxel synergistically kills human prostate cancer cells through the metabolic regulator AMP-activated kinase. Cancer Cell Int. 2019;19:1-14. DOI: 10.1186/s12935.019.0769-2

[75] Kahnert K, Kauffmann-Guerrero D, Huber RM. SCLC–state of the art and what does the future have in store? Clin Lung Cancer. 2016;17:325-333. DOI: 10.1016/j.cllc.2016.05.014

[76] Koinis F, Kotsakis A, Georgoulias V. Small cell lung cancer (SCLC): no treatment advances in recent years. Transl Lung Cancer Res. 2016;5:39-50. DOI: 10.3978/j.issn.2218-6751.2016.01.03

[77] Friedman JR, Perry HE, Brown KC, Gao Y, Lin J, Stevenson CD, Dasgupta P. Capsaicin synergizes with camptothecin to induce increased apoptosis in human small cell lung cancers via the calpain pathway. Biochem Pharmacol. 2017;129:54-66. DOI: 10.1016/j.bcp.2017.01.004

[78] Tung CL, Chen JC, Ko JC, Liu LL, Chien CC, Huang IH, Lin YW. Capsaicin acts through reducing p38 MAPK-dependent thymidylate synthase expression to enhance 5-fluorouracil-ınduced cytotoxicity in human lung cancer cells. Nat Prod Commun. 2021;16:1934578X21993335. DOI: 10.1177/1934578X21993335

[79] Mirabello L, Troisi RJ, Savage SA. International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons. Int J Cancer. 2009;125:229-234. DOI: 10.1002/ijc.24320

[80] Sadykova LR, Ntekim AI, Muyangwa-Semenova M, Rutland CS, Jeyapalan JN, Blatt N, Rizvanov AA. Epidemiology and risk factors of osteosarcoma. Cancer Invest. 2020;38:259-269. DOI: 10.1080/07357.907.2020.1768401

[81] Jin T, Wu H, Wang Y, Peng H. Capsaicin induces immunogenic cell death in human osteosarcoma cells. Exp Ther Med. 2016;12:765-770. DOI: 10.3892/etm.2016.3368

[82] Zhang Y, Deng X, Lei T, Yu C, Wang Y, Zhao G, Jiang D. Capsaicin inhibits proliferation and induces apoptosis in osteosarcoma cell lines via the mitogen-activated protein kinase pathway. Oncol Rep. 2017;38:2685-2696. DOI: 10.3892/or.2017.5960

[83] Wu D, Jia H, Zhang Z, Li S. Capsaicin suppresses breast cancer cell viability by regulating the CDK8/PI3K/Akt/Wnt/β-catenin signaling pathway. Mol Med Rep. 2020;22:4868-4876. DOI: 10.3892/mmr.2020.11585

[84] Lan Y, Sun Y, Yang T, Ma X, Cao M, Liu L, Liu Y. Co-delivery of paclitaxel by a capsaicin prodrug micelle facilitating for combination therapy on breast cancer. Mol Pharm. 2019;16:3430-3440. DOI: 10.1021/acs.molpharmaceut.9b00209

[85] Garufi A, Pistritto G, Cirone M, D'Orazi G. Reactivation of mutant p53 by capsaicin, the major constituent of peppers. J Exp Clin Cancer Res. 2016;35:1-9. DOI: 10.1186/s13046.016.0417-9

[86] Qian K, Wang G, Cao R, Liu T, Qian G, Guan X, Wang X. Capsaicin suppresses cell proliferation, induces cell cycle arrest and ROS production in bladder cancer cells through FOXO3a-mediated pathways. Molecules. 2016;21:1406. DOI: 10.3390/molecules21101406

[87] Bao Z, Dai X, Wang P, Tao Y, Chai D. Capsaicin induces cytotoxicity in human osteosarcoma MG63 cells through TRPV1-dependent and-independent pathways. Cell Cycle. 2019;18:1379-1392. DOI: 10.1080/15384.101.2019.1618119

[88] Bort A, Spínola E, Rodríguez-Henche N, Díaz-Laviada I. Capsaicin exerts synergistic antitumor effect with sorafenib in hepatocellular carcinoma cells through AMPK activation. Oncotarget. 2017;8:87684. DOI: 10.18632/oncotarget.21196

How to cite this article: Şanlıer N, Irmak E, Ejder ZB. The Relationship Between Capsaicin in Chili Pepper and Cancer: A Comprehensive Insight. Clin Exp Health Sci 2024; 14: 273-282. DOI: 10.33808/clinexphealthsci.1218885