

# An Updated Review On Anticancer Activity Of Capsaicin

Ali Al-Samydai , Farah Al-Mamoori , Hiba abdelnabi , Talal Aburjai

**Abstract:** Globally, cancer remains as one of the leading causes of morbidity and mortality. Although great advancements have been achieved in the treatment and control of cancer progression, significant short comings of the currently available treatment regimens pose serious challenges. Often, a number of undesired side effects occur during chemotherapy that is why, natural therapies, such as the use of plant-derived products in cancer treatment, may reduce the adverse side effects. Many plant-based products carry out multitargeting naturally are inexpensive and safe. Capsaicin is a naturally occurring alkaloid derived from chillies (*Capsicum annuum*, Solanaceae) that is responsible for its hot pungent taste. It is an odorless fat soluble compound. Capsaicin extracted from the fruit of the capsicum plant family.

It is a member of the vanilloid family of compounds such as vanillin from vanilla, eugenol from bay leaves and cloves, zingerone from ginger and Capsaicin from hot peppers. The vanilloids possess a vanillyl (4-hydroxy-3-methoxybenzyl) moiety and this confers their biological activity. Structurally, like other vanilloids, Capsaicin has a benzene ring and long hydrophobic carbon tail with a polar amide group. Recently, many research groups, including ours, found that capsaicin targets multiple signaling pathways, oncogenes and tumor-suppressor genes in various types of cancer models. In this review article, we highlight multiple molecular targets responsible for the anticancer mechanism of capsaicin.

**Index Terms:** Cancer, Tumorigenesis, Proliferation, *Capsicum annuum*, Capsaicin, phytochemical, *Invitro*, *In vivo*

## 1 INTRODUCTION

Globally, cancer remains as one of the leading causes of morbidity and mortality. Although great advancements have been achieved in the treatment and control of cancer progression, significant short comings of the currently available treatment regimens pose serious challenges [1],[2]. Often, a number of undesired side effects occur during chemotherapy that is why, natural therapies, such as the use of plant-derived products in cancer treatment, may reduce the adverse side effects [3]. Many plant-based products carry out multitargeting naturally are inexpensive and safe [4]. The overall incidence of cancer was significantly lower in regions where Indian spices are heavily consumed. One of the most used spices is hot chili peppers (*Capsicum annuum*.) that belong to the plant genus *Capsicum* (Solanaceae) [4], [5]. Many data now strongly indicates the significant anticancer benefits of Capsaicin "the active ingredient of *Capsicum annuum*" in various types of cancer models including pancreatic [6], prostatic [7], [8], liver [8], [9], bladder [10], [11] esophageal [12], leukemia [13], [14], lung [15], [16] endothelial cells [17], [18] and breast [19] [20]. but the limited systemic bioavailability may raise questions about the physiological relevance of their phytochemical effects *in vivo* [7]. Furthermore, Capsaicin is an extremely irritating compounds causing pain and burning on skin, mucosa and gastrointestinal side effect at even low concentrations [21], [22]

## 2 LITERATURE SEARCH METHODOLOGY

In this study, at first, the search was done by keywords such as "Capsaicin", or "cancer electronic databases such as Google Scholar, PubMed, Science Direct, etc. Related articles were selected for review.

a major public health problem worldwide with ~14 million new cases in 2012 and 8 million cancer-related deaths and is the second leading cause of death in the United States with 595,930 deaths occurring in 2015 alone [23]. By providing advances in cancer research, our knowledge of the cancer biological characteristics is updating every day. Cancer characterized by uncontrolled growth, spread of abnormal cells and dynamic altering in the genome (which cause cancerous features in normal cells) [24]. The cancer development impairs the normal biological process of healthy cells achieved by the invasion of nearby tissues and metastasize to distant tissues [25]. The common cancer treatments are surgery, radiation therapy, chemotherapy, combination therapy, and laser therapy. The selective therapies are based on the better conception of the biology and molecular genetics in the tumor progression used for the promising treatments [26]. In chemotherapy, by following the administration of a certain drug, a large number of patient tumor cells become resistant to the drug. So, drug resistance appears as a serious problem in the field of cancer treatment [26]. Ancient civilizations have used plants to cure a variety of human ailments. Even today, many people use higher plants as effective for the treatment of various diseases, Medicinal plants have proven, historically, their value as a source of molecules with therapeutic potential, and nowadays still represent a role as source of inspiration for novel drug compounds (leads). Since natural product-based drug discovery is associated with some intrinsic difficulties, the pharmaceutical industry has shifted its main focus toward synthetic compound libraries and high throughput screening for the discovery of new drug leads [27], [28]. The obtained results, however, did not meet the expectations as evidence in a declining number of deliver lead compounds in key therapeutic areas. As a result of that the interest in natural product-based drug discovery has revitalized in recent years [27], [28]. Cancer resistant is a global war; therefore, actions must be taken to reduce this problem. According to World Health Organization, medicinal plants would be the best source to obtain a variety of drugs [29]. Capsaicin figure 1 is a naturally occurring alkaloid derived from chillies (*Capsicum annuum*, Solanaceae) figure 2 that is responsible for its hot pungent taste. It is an odorless fat-soluble compound.

• Ali Al-Samydai\*, Farah Al-Mamoori, Hiba abdelnabi, Talal Aburjai1, Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Jordan, Amman, Jordan E-mail: Phalimahmoud2012@yahoo.com, \*Corresponding Author

Capsaicin extracted from the fruit of the capsicum plant family [30], [31]. It is a member of the vanilloid family of compounds such as vanillin from vanilla, eugenol from bay leaves and cloves, zingerone from ginger and Capsaicin from hot peppers. The vanilloids possess a vanillyl (4-hydroxy-3-methoxybenzyl) moiety and this confers their biological activity. Structurally, like other vanilloids, Capsaicin has a benzene ring and long hydrophobic carbon tail with a polar amide group. Recently, many research groups found that Capsaicin targets multiple signaling pathways, oncogenes and tumor suppressor genes in various types of cancer models as shown in table 1 [32], [33]. Also, Capsaicin has anti-angiogenic properties both in vitro and in vivo [18]. additionally, Capsaicin induced G0/G1 phase arrest in human esophageal carcinoma cells with an increase of p21 and a decrease of CDK4, CDK6 and cyclin E [34], [35]. and some study shown that treatment with Capsaicin also inhibited proliferation and induced cell cycle arrest in human cancer KB cells [18]. Also, Capsaicin significantly inhibited the migration of melanoma cells without leading to obvious cellular cytotoxicity. This effect was correlated with down-regulation of the phosphoinositide 3-kinase (PI3K) signaling cascade as well as a reduction in RAS related c3 botulinum toxin substrate 1 (RAC1) which is key kinase regulating cell motility and migration [36]. Friedman et al, study anticancer activity of natural and synthetic capsaicin analogs the applications of capsaicin, as a clinically viable drug are limited by its unpleasant side effects, such as gastric irritation, stomach cramps, and burning sensation. This has led to extensive research focused on the identification and rational design of second-generation capsaicin analogs, which possess greater bioactivity than capsaicin. A majority of these natural capsaicinoids and synthetic capsaicin analogs have been studied for their pain-relieving activity. Only a few of these capsaicin analogs have been investigated for their anticancer activity in cell culture and animal models. The present review summarizes the current knowledge of the growth-inhibitory activity of natural capsaicinoids and synthetic capsaicin analogs. Future studies that examine the anticancer activity of a greater number of capsaicin analogs represent novel strategies in the treatment of human cancers.

### 3. RESULTS AND CONCLUSION

The quest for developing anticancer principles from natural sources has a long historical track record and remarkable success stories. Capsaicin is a bioactive phytochemical abundant in red and chili peppers. Many studies have established cytotoxic activity of Capsaicin, the compound in chilli peppers with scientific name *Capsicum annuum* (Solanaceae), in various human cancer models. In most studies, capsaicin is a potential antitumor compound and the anticancer suppress BCa tumorigenesis by inhibiting its proliferation. additionally, capsaicin-reduced cell migration was associated with down-regulation of sirtuin 1 (SIRT1) deacetylase, possibly through proteasome-mediated protein degradation, cyclin D1 degradation and 20S proteasome activity could be the mechanistic target for anti-cancer activity of capsaicin in human colon cancer, capsaicin could significantly suppress cell growth, while changing histone acetylation in GC cell lines. Also, capsaicin decreases of hexokinase 2 (HK2) expression, which is known for its important role in tumor glycolysis capsaicin directly interacts with Src and inhibits Src activation to suppress the metastasis of LAC. father more, Capsaicin treatment induced the

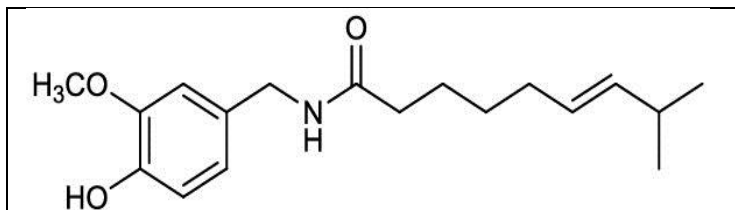
degradation of Tax and up-regulation of I kappa-B alpha, resulting in the decrease of nuclear factor (NF)-kappa B/p65 DNA binding activity. And capsaicin was potent cytotoxic compound to the androgen insensitive PC-3 cells and moderately cytotoxic to the androgen sensitive LNCaP cells, whereas it exhibited a very low cytotoxicity against the normal human prostate cell lines PNT2 and RWPE-1. on the other side, the clinical use of Capsaicin is handicapped by quick first pass metabolism and a short half-life of less than 8 min following intravenous administration, in addition to its poor bioavailability through oral administration that is mainly attributed to poor aqueous solubility. Furthermore, Capsaicin is an extremely irritating compounds causing pain and burning on skin, mucosa and has gastrointestinal side effect at even low concentrations. To tackle all above limitations of Capsicum annum (Capsaicin), developing a model carrier as nanogold or nanoliposomal, cyclodextrin may present a good solution. The global use of medicinal plants for the management of diseases, has promptly increased over the last decade [57].

<i>In-vitro(Cell line type)/In-vivo</i>	<i>Results</i>	<i>References</i>
<i>Bladder cancer</i>		
<i>invitro and in vivo</i>	<i>Capsaicin suppress BCa tumorigenesis by inhibiting its proliferation both in vitro and in vivo. Moreover, Capsaicin induced cell cycle arrest at G0/G1 phase and ROS production. strong increase of FOXO3a after treatment with CAP. Furthermore, they observed no significant alteration of apoptosis by Capsaicin, whereas Catalase and SOD2 were considerably up regulated, which could clear ROS and protect against cell death. Thus, results suggested that Capsaicin could inhibit viability and tumorigenesis of BCa possibly via FOXO3a-mediated pathways.</i>	[37]
<i>invitro T24 human bladder carcinoma cells</i>	<i>capsaicin-reduced cell migration was associated with down-regulation of sirtuin 1 (SIRT1) deacetylase, possibly through proteasome-mediated protein degradation. More importantly, they employed a cellular thermal shift assay (CETSA) to demonstrate that there was a direct binding between capsaicin and SIRT1. The engagement with capsaicin and protein degradation diminished the deacetylase of SIRT1, which in turn, enhanced acetylation of cortactin and <math>\beta</math>-catenin to decrease MMP-2 and MMP-9 activation, resulting in cell migration impairment in bladder cancer cells.</i>	[38]
<i>Colon cancer</i>		
<i>In-vitro (SW480, HCT116, LoVo and Caco-2)</i>	<i>In vitro data provide evidence that cyclin D1 degradation and 20S proteasome activity could be the mechanistic target for anti-cancer activity of capsaicin in human colon cancer.</i>	[39]
<i>Gastric cancer</i>		
<i>In-vitro (MGC-803)</i>	<i>capsaicin could significantly suppress cell growth, while changing histone acetylation in GC cell lines.</i>	[40]
<i>Esophageal squamous carcinoma</i>		
<i>In-vitro (ESCC cells)</i>	<i>Decrease of hexokinase 2 (HK2) expression, which is known for its important role in tumor glycolysis.</i>	[41]
<i>In-vitro (ESCC Eca109)</i>	<i>Capsaicin retrains the invasion and migration of Eca109 cells by inhibiting NF-<math>\kappa</math>B p65 via the AMPK-SIRT1 and the AMPK-I<math>\kappa</math>Ba signaling pathways, which cause MMP-9 expression inhibition.</i>	[42]
<i>Lung cancer</i>		
<i>In-vitro (SCLC)</i>	<i>Capsaicin improved the activity of calpain 1 and 2 by threefold relative to untreated SCLC cells.</i>	[43]
<i>Lung cancer</i>		
<i>In-vitro (LAC)</i>	<i>capsaicin directly interacts with Src and inhibits Src activation to suppress the metastasis of LAC.</i>	[44]

Table 1: Anticancer mechanism of Capsaicin (*Capsicum annum*, Solanaceae)

<i>In-vitro (Cell line type)/In-vivo</i>	<i>Results</i>	<i>References</i>
<i>Lung cancer</i>		
<i>In-vivo</i>	<i>Capsaicin-containing habanero pepper extract exhibits favorable effects on liver tumors in dogs and is well tolerated by the animals, thus the obtained results are a good sign for future studies on alternative medications used in dog oncology.</i>	[45]
<i>In-vitro (HCC)</i>	<i>Combining capsaicin and sorafenib significantly enhanced the suppression on cell proliferation, achieving a high-level synergistic effect (inhibition rates over 50%) and promoting HCC cell apoptosis.</i>	[46]
<i>Leukemia</i>		
<i>In-vivo</i>	<i>capsaicin effectively inhibited tumor growth and induced apoptosis in vivo using NOD/SCID mice with no toxic effects.</i>	[47]
<i>In-vitro (ATL)</i>	<i>Capsaicin treatment induced the degradation of Tax and up-regulation of I kappa-B alpha, resulting in the decrease of nuclear factor (NF)-kappa B/p65 DNA binding activity.</i>	[48]
<i>Melanoma cancer</i>		
<i>Human melanoma A375 and C8161 cell lines in vitro.</i>	<i>Capsaicin was demonstrated to exert a negative effect on cancer cell viability, and induced apoptosis of human melanoma A375 and C8161 cells via the activation of cleaved caspase -3 and PARP. Additionally, capsaicin -triggered autophagy contributed to cell survival by suppressing apoptosis of melanoma cells.</i>	[49]
<i>Ovarian carcinoma</i>		
<i>SKOV-3 ovarian cancer cells</i>	<i>CFLN showed a remarkably higher toxic effect compared to that of non-targeted nanoparticle system. CFLN showed significantly higher cancer cell apoptosis with nearly 39% of cells in apoptosis chamber (early and late) compared to only 21% and 11% for CLN and CAP.</i>	[50]
<i>Prostate cancer</i>		
<i>LNCaP and PC-3 prostate cells</i>	<i>capsaicin was a potent cytotoxic compound to the androgen insensitive PC-3 cells and moderately cytotoxic to the androgen sensitive LNCaP cells, whereas it exhibited a very low cytotoxicity against the normal human prostate cell lines PNT2 and RWPE-1.</i>	[51]
<i>LNCaP xenograft tumors</i>	<i>in vivo analyses revealed that the oral administration of physiologically relevant doses of capsaicin, when combined with radiation, is well tolerated, significantly reduces the tumor growth rate, and correspondingly alters NFkB and gH2AX expression in LNCaP xenograft tumors. These findings provide pre-clinical evidence supporting capsaicin as a novel radio-sensitizing agent for prostate cancer.</i>	[52]
<i>Renal carcinoma</i>		
<i>human renal cell carcinoma 786-O</i>	<i>Treatment of CPS reduced proliferation of 786-O cells and induced obvious apoptosis. These events were associated with substantial up-regulation of pro-apoptotic genes, while down-regulation of anti-apoptotic gene Bcl2. Furthermore, CPS significantly slowed the growth of 786-O renal cancer xenografts in vivo.</i>	[53]
<i>Thyroid cancer</i>		
<i>Human papillary thyroid carcinoma BCPAP cells</i>	<i>capsaicin treatment results in a decrease in cell migration and invasion of BCPAP cells, which were proven by both wound healing and trans well assays in vitro. Their results indicated that capsaicin inhibited the metastasis of BCPAP cells in a TRPV1-dependent manner.</i>	[54],

**Table 1:** Anticancer mechanism of Capsaicin (*Capsicum annuum*, Solanaceae)



**Figure1.** Molecular structure of capsaicin (=E)-N-(4-hydroxy-3-methoxybenzyl)-8-methyl-6-nonenamide). [55]



**Figure2.** hot chili paper plants [56]

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