Chapter

Anticancer Effect of Capsaicin and Its Analogues

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Abstract

Potent biomolecules from natural products from plants, animals, and minerals are the fundamental basis of the ailment of mankind. *Capsicum* or red pepper plants were grouped under the kingdom Plantae and family Solanaceae. It is used widely throughout the world in foods for their pungent flavor and aroma, and to prolong food spoilage. This chapter presents a frame of a concise compilation of the anticancer and cytotoxic potentials of *Capsicum*, its analogs, and related compounds. Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is the most predominant and naturally occurring alkaloid from the *Capsicum* species. It also details the anticancer efficacy of capsaicin and its analogs like capsaicinoids and capsiates which possess antioxidants and targets multiple signaling pathways, ontogenesis, and tumor-suppressor genes in various types of cancer models. Capsaicin is a major ingredient and has been linked to suppression of growth in various cancer cells. The data available strongly indicate the significant anticancer benefits of capsaicin and its potent analog molecules. It shows a significant effect on cancer cell proliferation, apoptosis, cancer cell surveillance, growth arrest, and metastasis. This chapter also predominantly focuses on the combinational use of capsaicin with other natural dietary compounds as a measure of synergistic anticancer activities.

Keywords: *Capsicum*, capsaicin, apoptosis, angiogenesis, metastasis, anticancer

1. Introduction

Capsicum is one of the most important genera in the Solanaceae family and consists of almost 30 species [1]. Their fruits were commonly referred to as peppers or chili peppers, having a bell shape that appears in different colors such as red, green, orange, and yellow. These have been commonly used in their diet by human society from ancient times as herb and spice. *Capsicum* is widely used as an essential ingredient in kitchens worldwide for their pungent flavor and scent and to prevent food contamination. It is known under many names, such as red pepper, chili pepper, paprika, tabasco, aji, cayenne, and tabasco jalapeno, because of its global consumption [2]. The genus *Capsicum* is comprised of various numbers of wild and few domestic species. The species domesticated are *Capsicum annum, C. baccalaureus, C. honey, C. frutescens, C. pudders,* in which *C. chinense* is the fruit with the highest pungency [3]. *Capsicum* has been documented for its wide range of activities, such as pain killers, cardiovascular protection, a cancer chemopreventive, and antioxidant effects. This chapter provides a comprehensive description of the capsaicin and its analogs as well as, more specifically, look into its therapeutic potential in various human cancer and future therapeutic directions of capsaicin.

2. Capsaicinoids

The chili-fruit pungent principles are called capsaicin. Capsaicin and many related compounds are called capsaicinoids. Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is a crystalline, lipophilic, colorless, and odorless alkaloid that is soluble in fat, alcohol, and oil. The major capsaicinoids or the analogs from *Capsicum annum* species are Capsaicin and 6,7-dihydrocapsaicin. The smaller capsaicinoids are nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin. Capsaicin and their analogs differ only in acyl group saturation [4, 5]. These alkaloids are produced solely by the genus *Capsicum*, and they are used as a potent analgesic for the treatment of pain and inflammation related to a number of diseases [6, 7].

Although capsaicin traditionally is associated with the analgesic activity, its unpleasant side effects, such as gastric irritation, stomach cramps, and burning sensation, limit capsaicin's applications as a clinically viable drug. This has led to extensive research focusing on the discovery and rational design of capsaicin analogs of the second generation, which have greater bioactivity than capsaicin. Modifications in the acid portion of capsaicin were found to generate analogs with different degrees of pungency. Three capsaicin analogs of two pungent and one with very low pungency were obtained by using multiple lengths of the acyl chain and chemical replacements in the aromatic ring [8]. The chemical structure of capsaicin and its analogs [9, 10] were shown in **Figure 1**.

Capsaicin (**Figure 1(1)**) and its analogs such as capsanthin (**Figure 1(2)**), capsanthin 3′-ester (**Figure 1(3)**), capsanthin 3′,3-diester (**Figure 1(4)**), capsorubin (**Figure 1(5)**), capsorubin 3′-ester (**Figure 1(6)**), and capsorubin—3,6-epoxide (**Figure 1(7)**) containing pharmaceutical products have been marketed under the trade name such as Menthacin, Zostrix, and Capzasin-P for topical applications. In 2009, the European Union (EU) and the USA Food and Drug Administration (FDA)

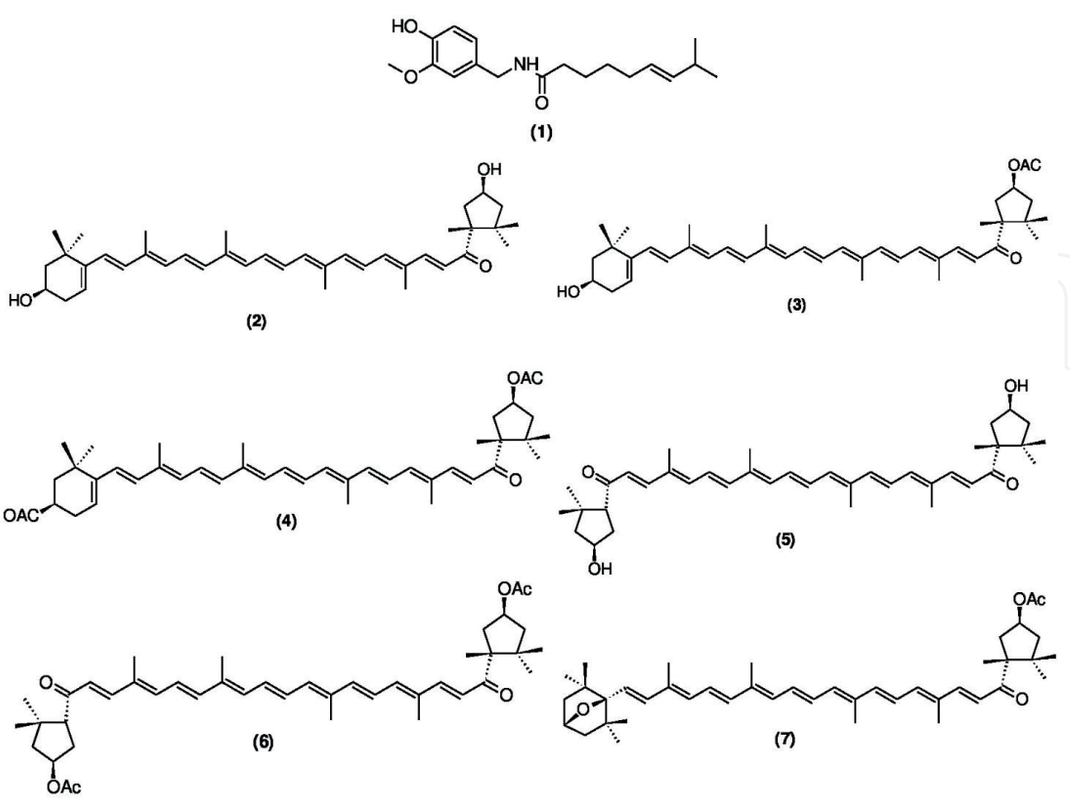

Figure 1.
*Capsaicin and its analogs: **(1)** capsaicin; **(2)** capsanthin; **(3)** capsanthin 3′-ester; **(4)** capsanthin 3′,3-diester; **(5)** capsorubin; **(6)** capsorubin 3′-ester; **(7)** capsorubin—3,6-epoxide.*

approved the use of capsaicin 8% patch (Qutenza or NGX-4010) for the treatment of post-herpetic neuralgia (PHN). Resiniferatoxin (RTX) is regarded as an ultra-potent analog of capsaicin that acts as an agonist of Transient receptor potential cation channel subfamily V member 1 (TRPV1) and displays several thousand-fold more potencies than capsaicin [11]. Zucapsaicin, the cis-isomer of capsaicin, shows potent efficacy against episodic cluster migraine prophylaxis, episodic cluster headache, and alleviates neuropathic pain [12]. Thus, capsaicin and its analogs have been used medicinally for centuries, but recently, it has been studied extensively for its analgesic, antioxidant, anti-inflammatory, anti-obesity characteristics and currently for its anticancer activity against a number of types of cancer [13]. It was witnessed by unparalleled advances in the field of capsaicin research. These studies and several other reports clearly showed that capsaicin and its analogs possess multiple pharmacological effects and its application in different clinical conditions.

3. Anticancer activity of capsaicin and its analogs

There is a strong epidemiological and experimental evidence that the phytochemical diet found in fruits, vegetables, whole grains, spices, and teas provides various inhibitory effects against the initiation, development, progression, and metastasis of cancer [14]. Capsaicin, a bioactive phytochemical abundant in chili peppers, is in between them. Capsaicin is a derivative of homovanillic acid, which has been shown to modify the function of many genes associated with cancer cell life span, growth arrest, angiogenesis, and metastasis [15, 16].

Tumorigenesis is a multistage process, which usually begins over an extended period. Cancer cells develop special properties not acquired by most healthy cells. Multiple genetic alterations and aberrant signaling pathways initiate and advance cancer. Determining the molecular targets involved in the tumor development process will provide opportunities to develop a successful cancer-fighting strategy. Studies assessing the capsaicin effect to inhibit cell proliferation by mechanisms are not fully understood in many types of cancer cells [17]. The capsaicin's suggested anticancer pathways include increased cell cycle arrest and apoptosis.

3.1 Capsaicin and apoptosis

Apoptosis is a vital mechanism against the growth of cancer, and it is strongly correlated with the loss of apoptotic signals in malignancy. It has been shown that capsaicin induces apoptosis in many different types of cancer cell lines, including pancreas, colon, prostate, liver, esophagus, bladder, skin, leukemia, lung, and endothelial cells, keeping the normal cells unharmed. A recent review noted capsaicin appears to induce apoptosis in more than 40 distinct lines of cancer cells [13, 18].

Two major signaling systems are the intrinsic mitochondrial death pathway and the extrinsic death receptor pathway, which activate executioner/effector caspases and lead to apoptosis. In specific, the mitochondrial pathway is involved in the complete execution of apoptosis; thus, the mitochondrion has been named as apoptotic mechanism's gatekeeper, and the mitochondrial death pathway proteins and pathways had become important targets for new treatments [19]. Many proteins involved in the mitochondrial death pathway have been targeted by capsaicin to induce apoptosis in different cancer cell lines. For instance, capsaicin treatment activated the cluster of differentiation 95 (CD95)-mediated apoptotic intrinsic and extrinsic pathways [20] and suppressed antiapoptotic protein expression, B-cell lymphoma 2, which causes caspase-9 and -3 activation, loss of mitochondrial membrane potential, and subsequent rises in cytochrome c release [21].

Capsaicin's proapoptotic activity has been found to be mediated via transient vanilloid potential receptor (TRPV1) in many types of cancers [21–23]. It is a nonselective cation channel pertaining to the transient receptor potential channel (TRP) family [24]. It does prefer Ca^{2+} to Na^{+}. Thus it contributes to changes in the concentration of cytosolic free Ca^{2+} and it is capsaicin's primary cell target.

3.2 Reactive oxygen species

Earlier research in pancreatic cells showed that the apoptosis effects of capsaicin were correlated with reactive oxygen species (ROS) production, c-Jun N-terminal Kinase (JNK) activation, mitochondrial depolarization, cytochrome c release in the cytosol, and caspase-3 cascade activation [25]. There is also quite a complex relationship that exists between capsaicin exposure and ROS production. ROS is conventionally considered cytotoxic and mutagenic in normal cells and can induce cell death, apoptosis, and senescence at high levels [26].

Capsaicin has been suggested to induce apoptosis in cancerous cells through the production of higher rates of intracellular ROS. This observation reveals capsaicin as the primary signaling molecule [27, 28]. Capsaicin is capable of activating apoptosis through nonreceptor mechanisms [25].

A number of studies in recent years have shown that oxidative stress causes cellular apoptosis through both mitochondria-dependent and mitochondria-independent pathways [29].

Mitochondria account for 50% of the total cytoplasmic volume in most cells and they participate more than any other organelle in metabolic functions, particularly those involved in cellular energy production. It also consumes nearly 90% of cellular oxygen and is the main source of ROS produced during breathing, and it is engaged in maintaining the intracellular redox state. Along with their long-standing role in energetics, mitochondria depict its prime focus in mammalian cells for many cell death signals. Interactions at the mitochondrion eventually determine whether a cell survives or dies in reaction to many physiological or therapeutic stimuli of cell death. A number of proteins involved in the mitochondrial death pathway were shown to be targeted by capsaicin in order to initiate apoptosis in various cancer cell lines.

It was reported that a 12-h exposure to high concentrations of capsaicin was necessary to induce higher apoptosis rates in Cellosaurus Colo 16 (COLO 16) cells [26]. More than half experienced apoptosis, which was correlated with progressive irreversible dispersion of mitochondrial transmembrane potential and elevated superoxide levels, illustrates the destruction of mitochondria and subsequent breakdown of mitochondrial electron transfer.

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is a part of the complex I of the mitochondrial electron transport chain. Capsaicin has been shown to specifically inhibit mitochondrial NADPH oxidase activity by competitively binding this enzyme to the ubiquinone/coenzyme Q site. Therefore, if capsaicin blocks the transportation of electrons in mitochondria, irreversible dispersion of mitochondrial transmembrane potential will occur. This will initiate apoptosis and change the mitochondrial permeability to release cytochrome c and eventual activation of proapoptotic pathways.

Capsaicin can block NAPDH oxidase in the plasma membrane by acting as a Q antagonist coenzyme. Capsaicin's vanillyl moiety is structurally similar to coenzyme Q's cyclic part, which could address the fact that vanilloids serve as antagonists to the coenzyme Q. Suppression of plasma membrane NAPDH oxidase was correlated with capsaicin's prooxidant and proapoptotic properties in some transformed cells, and activated T cells [30].

Another mechanism proposed by capsaicin's anticancer activity is interaction with AMP-dependent protein kinase (AMPK), which is the cell's primary metabolic gatekeeper, belonging to the family of protein kinase stimulated during enzyme-depleting metabolic states like hypoxemia, thermal shock, oxidative stress, and physical activity. It acts as a significant metabolic transition for maintaining energy homeostasis and shown to be an intrinsic controller of the mammalian cell cycle [31, 32].

There is an increase in intracellular Adenosine diphosphate (ADP)/Adenosine triphosphate (ATP) and/or Adenosine monophosphate (AMP)/ATP ratios [33] during energetic imbalance and it promotes activation of AMPK. Activation of AMPK increases oxidative stress in many human cancer cells and induces apoptosis. This stimulates catabolic pathways and, at the same time, inhibits the rate of anabolic reactions to regain the correct energy charge for adenylates.

Capsaicin treatment of human colorectal adenocarcinoma (HT29) cell line is shown to cause AMPK activation and inhibition of acetyl-CoA carboxylase (ACC), a well-known AMPK substrate, which indicates capsaicin inhibits lipid biosynthesis. The above concepts were implicated in apoptosis caused by capsaicin.

3.3 Capsaicin and cell cycle

The cycle of cells is a series of stages that cells undergo to allow them to divide and produce new cells. The cell cycle is divided into phases G0/G1, S, and G2/M stages. The cyclins, cyclin-dependent kinases (CDKs), and the CDK inhibitors are essential parts of the cell cycle. There are DNA checkpoints to assure DNA replication integrity. Such checkpoints and repair pathways render cellular responses to damage to DNA easier [14]. When stimulated, the CDKs provide the cells with a driving force to pass from one stage to the next, but if cyclin and/or CDKs are impaired, cell cycle arrest [17, 33, 34] happens. Thus, any alteration in these pathways raises the cancer risk. It was reported that capsaicin inhibits CDK2, CDK4, and CDK6 inhibiting the proliferation of 5637 bladder carcinoma cells via cycle arrest [34].

3.4 Capsaicin and p53

The p53 tumor suppressor prevents cell proliferation by inducing cell cycle arrest and apoptosis in response to cell stress such as damage to DNA, hypoxia, and activation of oncogenes. Phosphorylation is critical for p53-dependent transactivation at the Ser-15 residue [17]. P53 promotes apoptosis by a linear pathway involving Bax transactivation, cytosol-to-membrane Bax translocation, mitochondrial cytochrome c release, and caspase-9 activation, followed by caspase-3, -6, and -7 activation. Research studies indicate p53 is a target of capsaicin's anticancer action. Capsaicin was found to induce p53 phosphorylation of residue Ser-15 and enhanced p53 acetylation by sirtuin 1 downregulation, which is responsible for the initiation of apoptosis [35].

Incubated adenocarcinoma gastric cell line (AGS) of human gastric cancer with different capsaicin concentrations in the presence and absence of p53 siRNA showed that capsaicin induces apoptosis via p53 upregulation in AGS cells and that the apoptotic effect of capsaicin is p53-dependent [36]. It also observed that the tendency of capsaicin to induce the expression of proapoptotic proteins, such as Bax, caspase-3, and caspase-8, was almost entirely diminished by hitting down p53. Effects of capsaicin on the same cell type reported that caspase-3 activity increased with capsaicin exposure, indicating that capsaicin may serve as an anti-tumorigenic agent in human gastric cancer [37].

3.5 Capsaicin and β-catenin

β-catenin is a beneficial 90 kD protein that leads to cell growth under normal physiological conditions. It is a key transcription factor in the signaling of Wingless-Int (Wnt) and plays a vital role in stem cell regeneration and organ regrowth. Abnormal expression of β-catenin causes the malignant conversion of normal cells, and its anomalous activity has been documented in several cancer types. β-catenin is essentially active in many types of cancer cells. In a recent study, it was reported that capsaicin downregulated β-catenin transcription, decreased its protein stability, and caused apoptosis of colorectal cancer cells [38].

3.6 Capsaicin and angiogenesis

Angiogenesis is the development of new blood vessels from preexisting vasculature as well as an important homeostatic process for normal wound healing and embryonic growth. It involves the stimulation of endothelial cells, cell proliferation, invasion, chemotactic migration, and differentiation into new blood vessels [39]. Angiogenesis is a central player in cancer cell growth and tumor metastasis. The development of an angiogenic phenotype is regarded as a vital step in the progression of tumors [40, 41]. The cancer cells grew to 1–2 mm^3 in thickness in absence of circulation and stopped, but in the angiogenic area, they expanded beyond 2 mm^3. Tumors can become necrotic or even apoptotic in the absence of vascular support [42]. Thus, angiogenesis is a significant factor in cancer progression.

Some factors such as growth factors, cytokines, and vascular endothelial growth factor (VGEF) regulate angiogenesis. Nevertheless, VEGF plays a significant role in angiogenesis. In addition, endothelial cells produce growth factors that induce autocrine and paracrine growth of tumors. The initiation of angiogenesis correlates with the increased entry into the circulation of neoplastic cells and thus promotes metastasis [43]. Treatment of endothelial cells with capsaicin blocked the sprouting and development of VEGF-induced vessels in Matrigel mouse assay that was correlated with downregulation of p38 mitogen activated protein kinases (MAPK), protein kinase B (PKB), and focal adhesion kinase (FAK) activation [44, 45].

Furthermore, capsaicin enhanced deterioration of hypoxia-inducible factor1α, which is a crucial transcription factor rising VEGF transcription. Capsaicin thus interferes with typical angiogenic signaling pathways and can have the ability to suppress cancer becoming a malignant one. It was reported that capsaicin's anti-angiogenic activity was associated with reduced cyclin D1 expression, which results in decreased Rb phosphorylation, leading to the GI arrest of human endothelial cells of the umbilical cord (HUVEC) [46]. In addition, capsaicin also inhibited focal adhesion kinase (FAK) and p38 kinase activation caused by VEGF. All of the above results indicate that capsaicin is a dietary anti-angiogenic agent.

3.7 Capsaicin and metastasis

Cancer metastasis is the hallmark of tumor malignancy, which starts with the spread of cancer cells from the principal tumor to nearby tissues and distant organs, and it is the main cause of cancer morbidity and mortality. Metastatic cancer is resistant to treatment and contributes 80% of cancer-related deaths, which remains a great problem for cancer therapy [47]. Invasion and movement of tumor cells include the proteolytic degradation of extracellular matrix components by tumor cell-secreted proteases, involving serine proteases, plasminogen activators, and matrix metalloproteinases (MMPs).

Cancer type	Cell line	Effective doses (μM)	Anticancer mechanism
Human colorectal cancer	HCT 116	100–200	Induced autophagy
	LoVo, SW480	100	Induced anti-tumorigenesis; deregulation of β-catenin/TCF-dependent signaling
	Colo 205	150	Induced cell death, increased ROS, and proapoptotic proteins
Human breast cancer	MCF-7	50–300	Induced autophagy, inhibited growth, and induced apoptosis
	T47D, BT-474, SKBR-3	200	Inhibited growth and increased apoptosis
	MDA-MB231	20–200	Induced apoptosis and dysfunctions in mitochondria. Antiproliferative activity and arrest of cell cycle into G2/M phase. Enhances the apoptotic effects of TRIAL by activating the calcium-CaMKII-Sp1 pathway
Human prostate cancer	LNCaP	40–50	Inhibited proliferation and induced apoptosis
	PC-3	20–50	
	DU-145	500	
	RWPE-1	40	
Human myeloid leukemia	HL-60	>50	Induced G0/G1 phase cell cycle arrest and apoptosis
	U937, THP-1	200	Enhances the apoptotic effects of TRIAL by activating the calcium-CaMKII-Sp1 pathway
Human esophageal epidermoid carcinoma	CE 81 T/VGH	100	Induced apoptosis and G0/G1 phase cell cycle arrest
Human melanoma	A375	100	Inhibited cell growth and promoted apoptosis
Human KB cancer cells	KB cells	150–200	Reduced cell proliferation and viability. Induced cell death and cell cycle arrest in G2/M phase
Mouse melanoma	B16-F10	50	Inhibited cell migration. Induced apoptosis
Human pancreatic cancer	AsPC-1, BxPC-3	150	Inhibited proliferation. Induced apoptosis and generated ROS
	PANC-1	200	Induced G0/G1 phase cell cycle arrest and apoptosis; and inhibited growth
Human multiple myeloma	U266, MM.1S	>5	Inhibited cell proliferation, caused accumulation of cells in G1 phase
Human hepatoma	Hep G2	10–200	Decreased cell viability, generated ROS and activated caspase-3; and induced apoptosis and autophagy
	Hep3B	200	Enhances the apoptotic effects of TRIAL by activating the calcium-CaMKII-Sp1 pathway
Human nasopharyngeal carcinoma	NPC-TW 039	200–400	Induced G0/G1 phase arrest and apoptosis. Increased ROS
Human gastric carcinoma	SMC-1	200	Induced apoptosis
Human bladder cancer	T24	100	Induced ROS production and mitochondrial membrane depolarization

Cancer type	Cell line	Effective doses (μM)	Anticancer mechanism
Human small cell lung cancer	NCI-H69, NCI-H82, DMS53, DMS114	50	Suppressed growth in all four cell lines

TCF: T-cell factor; ROS: reactive oxygen species; TRIAL: TNF-related apoptosis-inducing ligand; CaMKII-Sp1: calcium-calmodulin-dependent kinase II signaling pathway I.

Table 1.
Anticancer potential of capsaicin against various cancer cell lines.

Capsaicin revealed its anti-invasive and anti-migratory activity by modulating signaling pathways including cell invasion and migration and suppressing advanced cancer stages. Treatment with capsaicin significantly reduced the metastatic burden in transgenic adenocarcinoma of the mouse prostate (TRAMP) mice. It has been reported that it significantly inhibited the migration of melanoma cells without leading to apparent cellular cytotoxicity [48]. This effect was associated with the downregulation of the signaling cascade of phosphoinositide 3-kinase (PI3 K) and reduction of the RAS-related c3 botulinum toxin substrate 1 (RAC1), which in itself is the main kinase controlling motility and migration of cells. Capsaicin blocked the invasion and migration of human fibrosarcoma cells triggered by epidermal growth factor (EGF) by downregulation of AKT/FAK, extracellular signal-regulated kinases, and p38 MAPK signaling, and subsequent downregulation of matrix metallopeptidase 9 (MMP9) in invasive fibrosarcoma cells.

Thereby, capsaicin recruits several mechanisms of signaling for controlling migration and invasion. These include epithelial-mesenchymal transition (EMT) activation, AMP-activated protein kinase (AMPK), MMP signaling pathway, intracellular calcium elevation, VEGF, Wnt-Hedgehog control, tumor-associated NADH oxidase (tNOX), protein kinase B (Akt), MMPs, epidermal growth factor receptor (EGFR), extracellular signal-regulated kinase (ERK), p38 MAP kinase, RAC1, nuclear factor "kappa-light-chain-enhancer" of activated B-cells (NF-kB), and AP-1 [49–54]. **Table 1** depicts the anticancer potential of capsaicin against various cancer cell lines.

4. Synergistic anticancer activity of capsaicin with other compounds

Recent development has allowed synergistic drugs to treat a wide array of cancers. Combinations of low doses of chemopreventive agents have progressively been used clinically in the treatment of various cancers in the present days. Compared to the traditional single drug policy, the combination strategy increases therapeutic effects or reduces drug resistance [55]. Computational progress in qualitatively testing and predicting synergistic components has been experienced in the last few years [56–58]. Multiple studies have illustrated that novel combination therapies with different phytochemicals and chemopreventive drugs can elicit increased antitumor activity through additive or synergistic action [59, 60].

The pathways can include parallel action on cancer suppression by modifying carcinogen detoxification and metabolism of hormones, scavenging oxidative stress, and enhancing immunity [61–63]. Hundreds of phytochemicals have various physicochemical and kinetic properties that target different signaling pathways and transcription factors that decide the phenotype of cancer. The use of several bioactive compounds with distinct anticancer pathways could, therefore, be a promising method for successful cancer treatment and prevention.

Capsaicin and other compounds are known to have synergistic anticancer properties. Combined with resveratrol, capsaicin facilitated apoptosis by elevating nitric oxide (NO) via a p53-dependent manner [64]. It has synergistic anticancer activity with pirarubicin, an anthracycline drug, by activating TRPV1 in bladder cancer [65]. Capsaicin shows a synergistic effect with the dietary phytoestrogen, genistein by regulation of AMPK and cyclooxygenase 2 in breast cancer cells [66]. Capsaicin and 3,3′-diindolylmethane, a key in vivo metabolite of indole-3-carbinol, abundantly present in cruciferous vegetables, have recently been reported to work synergistically to induce apoptosis in colorectal cancer, by altering the transcriptional function of the nuclear factor kappa B, p53, and control apoptosis-related genes [67]. Capsaicin, and brassinin, a form of indole derived from cruciferous vegetables, showed synergistic anticancer activity by suppressing MMP2 and -9 expression and enzymatic activities, and invasion, and migration of prostate carcinoma cells [68]. Sometimes, capsaicin also interacts with chemotherapy drugs. For example, in some myeloid leukemia cells [69], capsaicin enhanced the therapeutic efficacy with 12-O-Tetradecanoylphorbol-13-acetate. Capsaicin can, surprisingly, affect the viability of cancer stem cells. Capsaicin has been found to cause cancer stem cell death by inhibiting the NOTCH signaling pathway in stem cells of breast cancer [70].

5. Conclusion

An emerging cancer research area is the search for suitable molecular targets and effective anticancer compounds that modify the cancer targets. Capsaicin exhibits significant anticancer activity in various tumor stages by targeting multiple signaling pathways and cancer-associated genes. As a whole, capsaicin's anticancer pathways involve apoptosis initiation, cell growth arrest, and suppression of angiogenesis and metastasis. Capsaicin and its analogs activate the tumor-suppressive signaling pathway and associated transcription factors while inhibiting oncogenic signaling pathways and cancer cell promoters. In addition, capsaicin acts synergistically with other anticancer agents, allowing for the potential use of capsaicin with other chemotherapeutic agents in cancer therapy, and shows double advantage, i.e., capsaicinoids enhances the chemotherapeutic effect and pain relief for cancer patients. More research on capsaicin's and its analogs as anticancer targets holds the potential for future treatments and requires more study to improve our understanding of its efficacy in cancer treatment and prevention.

Conflict of interest

The authors have none to declare.

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