An updated review on molecular mechanisms underlying the anticancer effects of capsaicin

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Abstract: The quest for developing anticancer principles from natural sources has a long historical track record and remarkable success stories. The pungent principle of hot chili pepper, capsaicin, has been a subject of research for anticancer drug discovery for more than three decades. However, the majority of research has revealed that capsaicin interferes with various hallmarks of cancer, such as increased cell proliferation, evasion from apoptosis, inflammation, tumor angiogenesis and metastasis, and tumor immune escape. Moreover, the compound has been reported to inhibit carcinogen activation and chemically induced experimental tumor growth. Capsaicin has also been reported to inhibit the activation of various kinases and transcription that are involved in tumor promotion and progression. The compound activated mitochondria-dependent and death receptor-mediated tumor cell apoptosis. Considering the growing interest in capsaicin, this review provides an update on the molecular targets of capsaicin in modulating oncogenic signaling.

Keywords: capsaicin, chemoprevention, carcinogenesis, angiogenesis, detoxification, antioxidant, immunotherapy

Introduction

Capsaicin, (trans-8-methyl-N-vanillyl-6- nonenamide), is a pungent constituent of hot chili peppers (Capsicum frutescence L.) or hot red peppers (Capsicum annum L.) (1,2). Besides its use as a condiment, hot chili peppers are used in traditional medicine to ease neuropathic pain and reduce cholesterol level. Although capsaicin is mainly used as a therapy for peripheral neuralgia, there is a great deal of interest with the anticancer potential of the compound. The anticancer effects of capsaicin and its underlying molecular mechanisms have been extensively investigated over the last several decades. Whether capsaicin acts as a dietary carcinogenic mutagen or exerts antimutagenic and anticarcinogenic effects is debatable. The mutagenicity of capsaicin has been studied in both bacterial and mammalian cells in culture. Although early studies on capsaicin obtained from chili peppers provided conflicting reports of mutagenic and antimutagenic effects of the compound the use of synthetic and highly purified capsaicin in later studies revealed that the compound can protect against vinyl carbamate- or N-nitrosodimethylamine (NDMA)-induced mutagenesis in Salmonella Typhimurium TA100 partly by blocking the activity of cytochrome P450 2E1 (CYP2E1) (3). Subsequent studies have also revealed that synthesized pure trans-capsaicin does not cause mutagenicity in S. Typhimurium or Escherichia coli (4), but rather can suppress the metabolic activation of various heterocyclic amines, thereby limiting their mutagenic potential (5). Despite a few initial reports of capsaicin-induced genotoxicity, such as the formation of micronuclei in polychromatic erythrocytes, and increased frequencies of sister chromatid exchanges (6,7), the compound appeared to be non-genotoxic when used in its highest purity grade (8). Furthermore, capsaicin significantly attenuated cyclophosphamide-induced chromosomal aberrations and DNA strand breakages in mice (9), suggesting the anti-genotoxic effect of the compound.

Although several groups of researchers have reported capsaicin to be a carcinogen or a co-carcinogen, others have demonstrated that the compound possesses anticancer properties (10). The pioneering study by Park et al. (11,12) demonstrated that capsaicin not only lacks tumor promoting potential but rather inhibits 7,12-dimethylbenz[a]anthracene (DMBA)-initiated and 12-O-tetradecanoyl phorbol-13-acetate (TPA)-promoted mouse skin papillomagenesis. These findings have been supported by several other studies. For example, prolonged dietary administration of a mixture of capsaicin (64.5%) and dihydrocapsaicin (32.5%) did not exhibit any carcinogenic effects in B6C3F1 mice (13). In another study, treatment of v-Ha-Ras-transgenic (Tg.Ac) mice with TPA significantly increased skin tumor formation but treatment with capsaicin had no effect on tumor burden, suggesting that the compound lacks carcinogenic potential.
inhibited the microsomes isolated from capsaicin-treated Golden Syrian hamster function oxidases.

Role of capsaicin in the modulation of biochemical mechanisms implicated in cancer  Carcinogenesis, a multi-step process, involves three sequential phases of initiation, promotion, and tumor progression. Tumor initiation is a rapid and irreversible process that involves damage of cellular macromolecules, such as DNA, RNA, and proteins upon direct or indirect exposure to carcinogens. Tumor promotion is a reversible process involving clonal expansion of transformed cells to form benign tumors, which are premalignant in nature. Progression is the final stage of malignancy when the premalignant cells acquire the invasive and metastatic potential (15). Capsaicin can interfere with all stages of carcinogenesis (Fig. 1). The compound inhibits tumor initiation largely by blocking metabolic activation of carcinogens and fortifying cellular detoxification pathways, thereby protecting DNA from covalent modification and oxidative damage. The anti-tumor promoting effects of capsaicin are accredited to its ability to inhibit the induction of inflammation and tumor cell proliferation, and the induction of apoptosis in cancer cells. Capsaicin has been shown to block tumor progression by suppressing angiogenesis. Moreover, treatment with capsaicin enhances the sensitivity of various chemo-resistant cancer cells to existing chemotherapeutic agents. The following sections will focus on the mechanisms underlying the anticancer effects of capsaicin, with special focus on its molecular targets (Fig. 2).

Effects of capsaicin on phase I xenobiotic metabolizing enzymes  Phase I xenobiotic metabolizing enzymes cause bioactivation of various apparently inactive pro-carcinogens. The bioactivated carcinogens form covalent bonds with DNA, thereby resulting in direct DNA damage and the perturbation of intracellular signaling. Capsaicin has been shown to block the metabolic activation of various carcinogens. For instance, capsaicin attenuated arylhydrocarbon hydroxylase activity in human and murine keratinocytes, thereby blocking metabolic activation of BP and its subsequent interaction with DNA (16). Similarly, capsaicin inhibited the mutagenicity of tobacco-specific carcinogen NNK in S. Typhimurium TA100 by blocking its metabolic activation (17,18). NNK undergoes metabolic activation through α-carbon hydroxylation by microsomal mixed function oxidases. In vitro incubation of NNK with hepatic or pulmonary microsomes isolated from capsaicin-treated Golden Syrian hamster inhibited the α-carbon hydroxylation of NNK (18).

Capsaicin protected against vinyl carbamate- or N-nitrosodimethyl-lamine (NDMA)-induced mutagenesis in S. Typhimurium TA100 tester strain through the inhibition of CYP2E1 activity (3). However, capsaicin caused less than 20% inhibition of the CY2E1 activity in an in vitro test (19). According to the latter study, capsaicin inhibited the activities of CYP1A2, CYP2C9, and CYP2C19 with relatively low IC50 values (2.1–3.2 μM), and the activities of CYP2B6, CYP2D6, and CYP3A4 with relatively higher IC50 values (12–38 μM) in human liver microsomes (19). In contrast, daily oral administration of capsaicin to rats for seven days exhibited no significant effect on rat CYP1A2; however, it significantly inhibited the activity of CYP2C19 and induced that of CYP3A4 (20). While incubation of murine hepatoma Hepa-1c1c7 cells with capsaicin alone caused slight induction of CYP1A1 expression and activity, the compound inhibited 3-methyl cholanthrene (MC)-induced CYP1A1 levels through the activation of Ca2+/calmodulin-dependent protein kinase and CCAAT/enhancer-binding protein β (C/EBPβ) and inhibition of 3-MC-induced arylhydrocarbon transactivation. These findings suggest that the anticancer effect of capsaicin is mediated through the inhibition of expression and the activity of carcinogen metabolizing enzymes (21).

Modulation of cellular detoxification and antioxidant capacity  Cells have intrinsic ability to maintain an intracellular redox balance. A wide array of phase II detoxification/antioxidant enzymes facilitate elimination of metabolically activated carcinogens, thereby preventing reactive oxygen species (ROS)-mediated damage of cellular macromolecules. Capsaicin increased the protein expression and/or activities of various phase II detoxifying enzymes. The augmented activities of glutathione-S-transferase (GST) and quinone reductase by oral ministration of capsaicin protected F344 rats against chemically induced colon and tongue carcino genesis (22). The induction of another phase-2 enzyme heme oxygenase-1 (HO-1) has been reported to confer anticancer effects. Joung et al. (23) reported that