

## REVIEW ARTICLE

**The Dual Effects of Capsaicin: Benefits or Disadvantages?**

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**ABSTRACT**

Tastes consist of five basic tastes of taste (salty, sweet, bitter, sour, and umami) and five additional flavors (spicy, fat, calcium, water, and metal). In of the additional flavors, capsaicin is often found, consumed in daily life, and even considered as a candidate for alternative medicine. Capsaicin in general has the effect of a double-edged sword, with one side being positive and negative. Capsaicin's positive effects are effects that play a role in the process of maintenance body, such as: cardiovascular, body weight, gastrointestinal, pain reduction, inflammation, antibacterial, antibiofilms, and antivirals. While the negative effects revolve around its co-carcinogenic effects that are caused by two products released by capsaicin when stimulated and regarding the TRPV-1 agonist receptor, namely: Substance P (SP) and Calcitonin Related Genes Protein (CGRP). Both products are irritant, cause neurogenic inflammation, and trigger the activation of Mast Cells (MCs).

**Keywords:** Capsaicin, SP, CGRP, Anti-carcinogen, Co-carcinogenic

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**INTRODUCTION**

Taste consist of five basic flavors and additional flavors with this article will discuss one of additional flavors, which is spicy flavor (capsaicin) (1). Capsaicin (C<sub>18</sub>H<sub>27</sub>NO<sub>3</sub>) is a white, colorless, and odorless crystal that has monoclinic or rectangular shape, and is the main component found in hot peppers, which are: red chili peppers, jalapenos, and habaneros (2-6).

Capsaicin molecule has three areas: A area which is an aromatic part, B area which is an amide bond, and C area which is a hydrophobic bonding area. Area C is the most important area because it contains a hydrophobic group. Capsaicin agonists are Transient Receptor Potential Vanilloid-1 (TRPV-1) acts as integrators of several stimuli that cause pain and irritation and predominantly expressed in primary sensory neurons of C nerve fibers that are not myelinated in dorsal root ganglion (DRG) and trigeminal ganglia (TG) (7,8,9).

**LITERATURE****Description Concept, Chemical Formula, and Capsaicin Agonist Receptor**

The capsaicin agonist is TRPV-1 functions as an integrator of several stimuli and causes pain and irritation. TRPV-1 is predominantly expressed in primary sensory neurons of C nerve fibers that are not myelinated and have stomata in DRG and trigeminal ganglia (TG). Neuron fibers of peripheral nerve will transmit noxious stimulation (nociceptors) and become a place of pro-inflammatory neuropeptides release that initiates neurogenic inflammatory processes cascade. The main axons enter central nervous system (CNS) which then synapses with second-order neurons in dorsal horn spinal cord (DRG neurons or trigeminal tract spinal nucleus (TG neurons). The binding of capsaicin to non-selective TRPV-1 receptor lies within sensory nerve endings, and is a primary afferent fiber with small nerve diameter (10,11).

**Positive Effect Concept of Capsaicin**

Capsaicin might also offer protection from cancer, but this effect is a double-edged sword effect which on one side gives a positive effect and on the other hand gives a negative effect. Apoptosis is a programmed

cell death and is needed to maintain physiological balance, therefore it plays an important role in preventing cancer development and progression (malignancy). Apoptosis occurs through two main pathways, which are intrinsic pathway (mitochondria) and extrinsic pathway. Extrinsic pathway begins with stimuli that induce death-inducing signaling complex (DISC) formation and caspase 8 activation. Intrinsic pathway begins with a variety of intracellular signals resulting in mitochondrial disruption and altered Bcl-2 protein family regulation that results in pro-apoptosis (cytochrome-c and apoptosis-inducing factor/AIF) release from mitochondrial intermembrane cleft to cytosol. Capsaicin could mediate apoptosis process and prolong p53 gene life time by increasing transcriptional activity, phosphorylation, and increasing p53 gene acetylation. p53 gene plays an important role in maintaining genomic integrity and is often known as “the guardian of genome, the guardian angel of gene, and the master watchman” (12).

### Negative Effect Concept of Capsaicin

Capsaicin application on skin or mouth mucosa will cause a local burning sensation which is followed by a state of allodynia and hyperesthesia due to mechanical stimulation and heat. Nociceptive effect is associated with neurogenic inflammatory response that is triggered by neuropeptide release from free nerve endings, such as SP and CGRP which are known to be neurogenic inflammatory neuropeptides. SP actually acts on micro vascularization via neurokinin-1 receptor (NK-1). It has vasodilating effect, increases vascular permeability, triggers pro-inflammatory cytokines release (13).

### DISCUSSION

Capsaicin is called a “double-edged sword” because on one hand it has several positive effects, but on the other hand it is known as co-carcinogenic factor caused by SP and CGRP which are released when sensitized. The positive effect of capsaicin is due to its role in inducing apoptosis through intrinsic and extrinsic pathways as well as triggering Reactive Oxygen Species (ROS) production at cellular level in cancer cells and inhibiting NF-KB transcription factor which is involved both malignancy and inflammation. Another capsaicin mechanism against cancer is that it could suppress Vascular Endothelial Growth Factor (VEGF) through its receptor, Hypoxia Inducible Factor-1 (HIF-1). Capsaicin role against inflammation is through active anti-inflammatory component of capsaicin might activate TRPV-1, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), interleukin-12 (IL-12), and interleukin-1 $\beta$  (IL-1 $\beta$ ). Inflammatory disease is related to human’s immune response, both innate and adaptive immunity. Capsaicin has an effect on immune system, for example on IL-1 $\beta$  expression and on toll like receptor-4 (TLR-4) by

suppressing IL-1 $\beta$  production. IL-1 $\beta$  is induced by NF-KB transcription factors and toll-like receptors (TLRs) or RIG-like receptors (RLRs) stimulations. Capsaicin application on the skin or mouth mucosa causes local burning sensation followed by a state of allodynia and hyperesthesia. Nociceptive effects are associated with neurogenic inflammatory responses that are triggered by neuropeptides release from free nerve endings, such as SP and CGRP.

CGRP and SP release from free nerve ending also triggers MCs activation which have important effects in inflammatory reactions and induces microvascular dilatation followed by increased blood flow (14).

### CONCLUSION

In conclusion, capsaicin is a double-edged sword, on one hand it has positive effect as anti-cancer by extending p53 gene life time and negative effects because it could interact with epidermal growth factor receptor (EGFR).

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