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Unveiling the Multifaceted Roles of Capsaicin: From Sensory Mechanisms to Therapeutic Potential

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Abstract: The active component of chili peppers' fiery heat, known as capsaicin, can be used to develop new knowledge about metabolism, pain, and cancer prevention. Despite the progress that has been made in studying its effects, the full potential of this substance remains unconquered. The review presents a comprehensive overview of recent discoveries related to the physiological effects of capsaicin. It mainly focuses on its molecular mechanisms that trigger the burning sensation. It also covers the antioxidant and metabolic properties of this compound. Not only does it provide a broad overview of the current state of the art in the study of capsaicin, but it also offers valuable recommendations for future endeavors.

Keywords: capsaicin, TRPV1, metabolic effect, antioxidation

1. Introduction

The origin of chili peppers can be traced back to South America, which is over 6,000 years old.[1] They have since undergone various transformations and have now become widely used in various cuisines all around the world. Aside from being used as a seasoning, chili peppers are also widely used as a source of vitamin C. They can be pickled or dried, and they can be processed into different forms of food products such as chili sauce, dried chili powder, and chili oil. Even chili seed oil is edible and widely utilized.

The average annual production of chili peppers is about 4.7 million pounds. This amount is currently valued at about $100 million.

The popularity of chili peppers can be attributed to their unique taste. However, not everyone can cope with their distinct spiciness. In our daily lives, people have varying levels of tolerance to the heat of these peppers. Unfortunately, there is a lack of research regarding the causes of this phenomenon, making it hard for people to understand why they can tolerate different levels of spiciness.

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2. Capsaicin is the major constituent of chili pepper

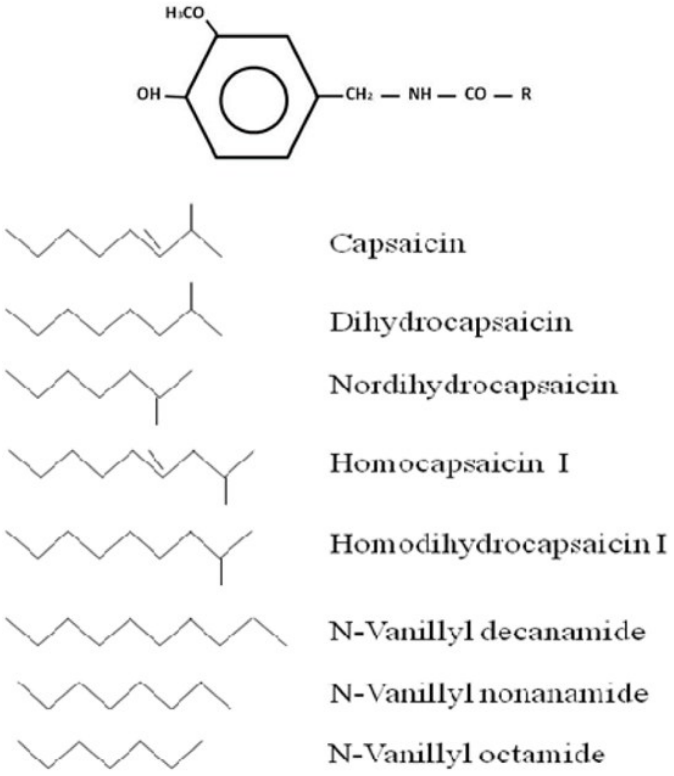

Figure 1: Chemical structure of different capsaicinoids and their analogues.

It has been widely believed that the main constituent of chili peppers is capsaicin. There are various other compounds known as nordihydrocapsaicin, dihydrocapsaicin, or homocapsaicin, which also share similar structures. These compounds are believed to exert similar effects on the body (Figure1). The main component of capsaicin is a benzene ring, which is joined by a polar amide group and a hydrophobic carbon tail. It exhibits trans/cis isomerism due to its double bond, which prevents its internal rotation. The trans isomerism of capsaicin is due to its double bond. This prevents its internal rotation. In the cis form, the long chain and the -CH(CH3) will be near each other, which will cause slight repulsion. This is because the steric hindrance will prevent the two compounds from repelling each other. Due to the additional strain introduced to the cis isomer, it has a less stable configuration. (Figure2)[2]

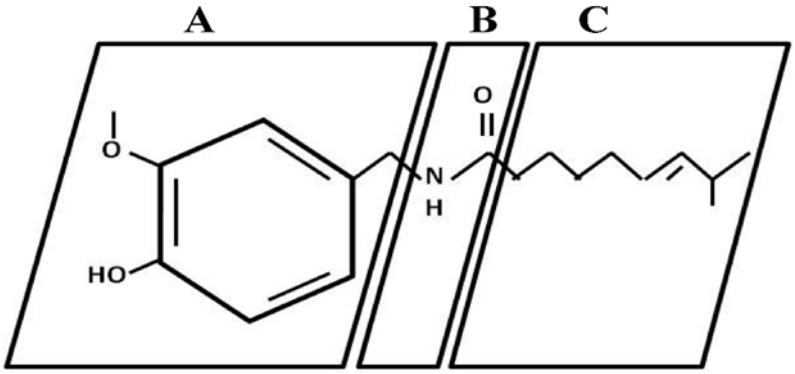

Figure 2: Regions of the molecule of capsaicin. A (aromatic ring); B (amide bond); and C (hydrophobic side chain).

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The alkaloid capsaicin is responsible for the distinctive burning sensation that chili peppers produce. It can trigger various physiological responses and has poor absorption.[3] It is an odorless, pungent, and fat-soluble substance that has a melting point of around 62-65 degrees Celsius. Due to its non-water soluble nature, alcohols and certain organic solvents are commonly used to soludate and prepare topical sprays and other products.[4] Although chili peppers are known to contain various nutrients, such as vitamins C and A, they are not as relevant to our discussions as other compounds such as minerals and inorganic salts.

3. Physiological effects of Capsaicin

3.1. TRPV1 and the burning sensation

As part of the nonselective cation channel family, the TRPV1 is capable of responding to chemical and physical stimuli. Their role in the various processes involved in calcium and sensory transduction is acknowledged. Understanding how the body's various channels respond to physiological or drug stimuli is important in developing a more accurate understanding of how different disorders affect the body's organs. Somatosensory cells and other sensory cells can sense temperature changes within the environment with the help of these channels.[5]

TRPV1 is mainly expressed by trigeminal ganglion (TG) neurons and small-diameter neurons within sensory ganglia, such as the dorsal root ganglion (DRG). It was first identified as a polymodal receptor[6], responding to stimuli of different natures such as noxious heat(>43℃) and capsaicin, the pungent compound present in hot chili peppers that functions as a chemical agonist of the channel, eliciting pain-associated behaviors in animals and pain in humans.[7] Research has shown that the interaction between the TRPV1 channel and capsaicin triggers an opening in the membrane channel. This allows the presence of potassium and calcium ions to enter the sensory cells, which then produces a nervous impulse. The resulting sensation is then transmitted to the part of the brain that processes sensory information. It has been suggested that the variations in the sensations experienced by individuals when eating chili peppers may be caused by the variations in the number of receptors of the TRPV1 channel.

3.2. Method for alleviating capsaicin-induced pain

Studies have shown that prolonged exposure to capsaicin can desensitize the neurons in mice, decreasing their ability to respond to certain stimuli. It is believed that this phenomenon, which can be reversible, is caused by the depletion of an unknown substance. This can lead to the reduction of pain sensitivity.[8] The FDA has approved the use of 8% topical patches containing synthetic forms of the chemical known as Capsaicin. Each patch contains a total of 179mg of this substance. A study conducted on the effects of this patch on various types of neuropathic pain has shown that it can effectively manage these conditions. The study conducted on subjects experiencing chronic pain showed that their pain levels decreased, sleep duration was improved, and they had reduced reliance on anti-epileptic drugs and opioids[9] .

3.3. Metabolic effect of capsaicin

Studies on the effects of dietary or topical application of capsaicin on high-fat mice have shown that it can enhance the growth of PPAR and reduce visceral fat mass and weight gain. In addition, one study revealed that the chemical transformed the expression of connexin-43 and hormone-sensitive lipase in the animal's tissues. The development of lipolysis is dependent on the ability of adipocytes to communicate with one another, and the presence of Connexin-43 can play a crucial role in this

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process. In addition, exposing mesenteric tissues to capsaicin can increase the protein's expression.[10].

The beneficial effects of capsaicin on metabolic syndrome in mice may be partly mediated by an increase in the secretion of glucagon-like peptide-1 (GLP-1). Research has demonstrated that gastric administration of capsaicin stimulates the gastrointestinal (GI) tract to secrete more GLP-1, leading to elevated plasma levels of this hormone. Notably, this effect is absent in TRPV1 knockout mice. It is proposed that the enhancement in GLP-1 secretion may be mediated by increased calcium influx into intestinal L cells.[10].

Capsaicin and its constituent, capsiate, can help balance the energy expenditure and oxidation of fat, suppressing appetite and reducing fat mass. However, these effects may also be accompanied by various side effects, such as soreness in the oral cavity. Because of this, caution should be taken when considering this substance as a weight-loss supplement..[11].

3.4. Contribution of the digestive system

It is commonly believed that spicy foods can cause gastrointestinal issues. However, recent studies challenge this notion. A clinical study found that gastric tissue damage and micro bleeding induced acutely by indomethacin or ethanol ingestion were significantly reduced when capsaicin was administered concurrently. Current evidence suggests that topical NSAIDs and capsaicin, when used at approved doses, may provide comparable pain relief for osteoarthritis (OA). However, whether this equivalence varies between individuals remains unknown.[12] These findings have led to the suggestion that capsaicin could be used as a protective adjunct to non-steroidal anti-inflammatory drug (NSAID) therapy.[10]. Limited epidemiological evidence suggests that gastric ulcers may be less common in ethnic groups that favor spicy foods.[13] .

4. Medical values of chili pepper

4.1. Antioxidation

Chili peppers are rich in antioxidants, including vitamins C and A, carotenoids, flavonoids, and other polyphenols. Lee et al proposed that capsaicin is a potent antioxidant, capable of lowering low-density lipoprotein (LDL) levels even with short-term consumption. They also found that capsaicin (CAP) improves the antioxidant status of both blood and the brain. Anandakumar et al. highlighted CAP's role in mitigating oxidative stress-induced damage during lung cancer. In terms of antioxidant efficiency, Henderson and Slickman found that CAP is more effective than melatonin in suppressing the formation of lipid hydroperoxides, while Kogure et al. reported that CAP inhibits lipid peroxidation more efficiently than α-tocopherol. [14].

4.2. Immune system

Pigments such as β-cryptoxanthin, neoxanthin, zeaxanthin, capsanthin, capsorubin, and lutein have been investigated for their potential roles in cancer treatment and prevention. Several studies have demonstrated that these pigments can attenuate oncogene signaling, induce apoptosis in cancer cells, regulate cell cycle progression, modulate redox balance, inhibit tumor-specific angiogenesis, control tissue invasion and metastasis, and influence gap junction intercellular communication, as well as multidrug resistance.[15] Capsaicin promotes tumor progression through mechanisms such as increased cell proliferation, evasion of apoptosis, inflammation, tumor angiogenesis, metastasis, and immune escape. Additionally, it has been reported to inhibit carcinogen activation and suppress chemically induced tumor growth in experimental models. Capsaicin has also been shown to inhibit the activation of various kinases and transcription factors involved in tumor promotion.

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Activation of TRPV1 leads to the recruitment of catecholaminergic neurons in the rostral ventrolateral medulla of the brain. This catecholamine release has been linked to some of capsaicin's weight-modifying effects. A study by Yoshioka et al. demonstrated an increase in diet-induced thermogenesis and lipid oxidation when a high-fat diet was combined with capsaicin. Subsequent research by various investigators supported these findings, showing enhanced energy expenditure following capsaicin intake. Among these studies, Lejeune et al., Josse et al., and Lee et al. reported an increase in lipid oxidation, while Ludy and Mattes observed a reduction in appetite. Topical application of capsaicin has also been shown to increase the expression of adiponectin and other adipokines, thereby reducing fat accumulation in the adipose tissue of obese mice. In contrast, studies by Smeets and Westerterp-Plantenga, as well as Galgani et al., found no effect of capsaicin on energy expenditure or lipid oxidation, highlighting variability in responses across different populations.[9]

4.3. Clinical uses

Capsaicin has a broad range of clinical applications, including the relief of nausea, vomiting, pruritus, and myocardial ischemia following surgery, demonstrating notable therapeutic effects. Additionally, capsaicin has been shown to alleviate postoperative sore throat by stimulating acupoints.

The use of antibiotics often reduces the diversity of intestinal flora. However, capsaicin intake has been shown to reverse this effect by increasing the content of acetate. Additionally, capsaicin can influence the microbiome and related metabolic pathways, particularly by increasing the abundance of opportunistic pathogens and promoting metabolic processes such as arachidonic acid metabolism and lipopolysaccharide biosynthesis. However, excessive or indiscriminate use of capsaicin in the environment may lead to intestinal inflammatory responses and other adverse effects. Therefore, moderate capsaicin consumption during antibiotic treatment may offer potential benefits for maintaining intestinal health, but should be approached with caution. [9]

Recent research has also shown that capsaicin effectively reduces blood lipid levels, particularly serum triglycerides, total cholesterol, and low-density lipoprotein (LDL), while increasing high-density lipoprotein (HDL) cholesterol levels. Capsaicin regulates lipid metabolism through multiple pathways, including modulating the expression of proteins related to lipid metabolism in liver tissue. As a result, capsaicin, in combination with rutin, demonstrates a strong synergistic effect in lowering lipid levels, making it a promising candidate for the development of new lipid-lowering drugs.[16]

Investigations into the antifungal properties of capsaicin, particularly against Candida albicans, a common cause of oral candidiasis, have yielded promising results. Nascimento et al. reported that capsaicin, at a minimum inhibitory concentration (MIC) of 25 μg/ml, effectively inhibited the growth of C. albicans. Furthermore, Omolo et al. demonstrated that C. albicans exhibited greater susceptibility to capsaicin compared to certain bacterial strains. Behbehani et al. proposed a mechanism for capsaicin's antifungal activity, suggesting that it disrupts C. albicans cell wall integrity by inhibiting ergosterol biosynthesis. Additionally, the combination of capsaicin and fluconazole showed enhanced efficacy, potentially helping to prevent the development of fluconazole resistance.[17]

Recent research has shown that capsaicin can alleviate symptoms of salt-sensitive hypertension, including high blood pressure, tachycardia, and structural damage to the heart and blood vessels. The mechanism of capsaicin's effects may be linked to its activation of the AMPK-AKT-NRF2 pathway. Additionally, capsaicin may inhibit the expression of proinflammatory cytokines and modulate the PI3K-AKT-NF-κB signaling pathway. Therefore, capsaicin holds potential as a novel therapeutic strategy for the treatment of salt-sensitive hypertension.[18]

Moreover, capsaicin is believed to have therapeutic potential in treating pulmonary fibrosis. Studies have highlighted its efficacy in alleviating the harmful effects of bleomycin, a potent anticancer agent known to induce dose-dependent pulmonary fibrosis. Our findings reveal that

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capsaicin treatment significantly improves both the macroscopic and microscopic characteristics of lung tissue affected by bleomycin.

Intratracheal administration of bleomycin resulted in visible signs of fibrosis, histopathological alterations, increased collagen deposition, elevated mucin content, inflammatory cell infiltration, and upregulated fibrosis markers such as hydroxyproline, α-SMA, and TGF-β1. Bleomycin also induced inflammatory markers like TNF-α, IL-1β, IL-6, NF-κB, and COX-2, along with oxidative stress markers including NO, MDA, and protein carbonyl. Additionally, bleomycin compromised anti-inflammatory and antioxidant mechanisms, as evidenced by decreased expression of PPAR-γ and Nrf-2, reduced GSH levels, total antioxidant capacity, and activities of catalase and SOD.

In contrast, capsaicin treatment following bleomycin exposure improved lung tissue morphology and reversed histopathological changes compared to the approved antifibrotic drug pirfenidone. These effects were evident in the form of reduced collagen deposition, lower fibrosis scores, decreased mucin content, reduced inflammatory cell infiltration, and downregulated levels of fibrosis markers (hydroxyproline, α-SMA, and TGF-β1). Capsaicin also suppressed inflammatory markers (TNF-α, IL-1β, IL-6, NF-κB, and COX-2) and oxidative stress markers (NO, MDA, and protein carbonyl). Furthermore, capsaicin enhanced anti-inflammatory and antioxidant pathways (PPAR-γ, Nrf-2, GSH, total antioxidant capacity, and catalase and SOD activities), showing efficacy comparable to pirfenidone.[19].

4.4. Cancer treatment

Capsaicin-induced apoptosis in pancreatic cancer cells has been shown to be triggered by disruption of the mitochondrial membrane potential. Additionally, it was demonstrated that capsaicin reduces the activity of several key antioxidant enzymes, including catalase, glutathione peroxidase, and superoxide dismutase. Furthermore, while capsaicin has no effect on healthy cells, it inhibits electron transport chain complexes I and III in cancer cells. Recent research on pancreatic cancer has also shown that capsaicin stimulates caspase-3, induces G0/G1 phase cell cycle arrest, and reduces cancer cell survival in a dose-dependent manner. Studies using prostate cancer cell lines have shown that capsaicin inhibits the activity of nuclear factor-kappa B (NF-κB) and tumor necrosis factor-alpha (TNF-α), both of which play critical roles in inflammation and cancer progression. In the human pancreatic cancer cell line PANC-1, capsaicin induces cell death through the activation of the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway. These findings suggest that capsaicin has significant potential as an anticancer agent across various cancer types, including hepatocellular carcinoma, colon cancer, gastric cancer, breast cancer, and leukemia.[20].

5. Conclusion

This study highlights capsaicin as a multifaceted compound with significant implications for both scientific research and practical applications. The varying levels of tolerance to capsaicin's heat are largely attributed to genetic differences in TRPV1 protein expression, underscoring the importance of individual variability in sensory perception. Beyond its sensory effects, capsaicin demonstrates considerable health benefits, including its roles in metabolism, antioxidation, and potential therapeutic applications, particularly in pain management and cancer prevention.

While the existing body of research provides valuable insights, it also reveals gaps that warrant further investigation. Unresolved questions, such as the precise mechanisms underlying capsaicin's effects on the nervous and metabolic systems, highlight the need for deeper theoretical exploration and experimental validation. Future studies should aim to bridge these gaps by employing advanced techniques and diverse populations, ensuring a broader understanding of capsaicin's impact.

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In conclusion, capsaicin offers promising avenues for research and innovation, from its potential use in clinical treatments to its applications in nutrition and health. By addressing current limitations and building upon the findings presented, future research can unlock new dimensions of capsaicin's benefits, contributing to advancements in science, public health and disease treatment[21]. These evidences suggest that chili peppers, which are rich in carotenoids, could be developed into novel anti-cancer drugs.

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