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REVIEW ARTICLE

Unlocking the Power of Capsaicin: A Comprehensive Review of Its Mechanisms and Applications

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Abstract

Capsaicin is the main bioactive compound in chili peppers (*Capsicum* sp.) that has attracted widespread attention in pharmacology and health. This substance functions by stimulating the Transient Receptor Potential Vanilloid 1 (TRPV1) receptor, which is involved in the sense of pain, the control of body temperature, and inflammatory reactions. This study reviews the mechanism of action of capsaicin and its applications in various fields of health and clinical therapy. Capsaicin has diverse pharmacological effects, including as an analgesic, antioxidant, cardioprotective, anti-cancer, and metabolic regulator agent in the management of obesity. In addition, this compound shows potential in neurodegenerative therapy, such as Alzheimer's and Parkinson's diseases, by reducing oxidative stress and neuroinflammation. Capsaicin also has gastroprotective, dermatoprotective, antimicrobial, and anti-inflammatory effects, making it a potential ingredient in various medical applications. However, side effects such as gastrointestinal irritation, burning sensation, and possible long-term toxicity need to be considered in its use. Therefore, further research is needed to develop safer and more effective formulations. In addition to its medical applications, capsaicin is also used in the food and biotechnology industries. With a deeper understanding of its mechanisms of action such as affecting the nervous system, body fat profiles, and controlling hunger and other mechanisms described in this paper, capsaicin has the potential to be an important component in the development of molecular-based therapies. Further studies are needed to optimize its therapeutic benefits and explore its safety in broader clinical applications.

Keywords: Capsaicin, Clinical use, Good health and wellbeing, Pharmacology, TRPV1

Introduction

Chili (*Capsicum* sp.) is a common food crop and medicinal herb used around the world. It can be either an annual or a limited perennial plant [1]. A classic spice plant, chilies are high in capsaicinoids, carotenoids, vitamins, and minerals [2]. Chili plants produce the most prevalent spicy chemical, capsaicin, which is an essential element in spicy cuisines consumed throughout the world [3]. Capsaicin, a member of the well-known vanilloid family, has drawn a lot of interest from the scientific community due to its numerous bioactive qualities and wide spectrum of pharmacological effects [4]. When this material comes into touch with the tissues of mammals, it creates irritation and a burning feeling [5]. Large amounts of capsaicin are present in the placental tissue that contains the fruit's seeds [6].

The natural alkaloid capsaicin, whose chemical name is Trans-8-methyl-N-vanillyl-6-nonenamide ($C_{18}H_{27}NO_3$), is taken from the fruit of the capsicum plant [7]. In the vacuoles of the red pepper placenta's epidermal tissue, this compound is produced by 8-methyl-6-nonenoyl-CoA and vanillamine with the help of capsaicin synthase (CS) [8]. Capsaicin is another plant metabolite product with a biosynthesis pathway, specifically through 2 pathways: fatty acid metabolism, which determines the fatty acid molecules that are also crucial to comprehending a metabolite product, and the phenylpropanoid pathway, which determines the phenolic structure [7,9]. The current name for capsaicin was given by John C. Thresh in 1876 after it was initially isolated (in impure form) by Christian F. Bucholz in 1816 [10]. The idea of "treating like with like" or counteracting irritation has been the basis for the homeopathic use of capsaicin since its discovery to relieve searing pain [11].

The crystalline and lipophilic compound capsaicin is typically a pale white solid with a melting point between 62 and 65 °C and a molecular weight of 305.4 kDa. At 25 °C, it exhibits stability in both basic and acidic environments [12]. The structural features of capsaicin, which include a benzene ring and a long hydrophobic carbon tail with a polar amide group, make it soluble in fat but insoluble in water [4]. It is soluble in acetone, ethanol, methanol, chloroform, and alkaline aqueous solutions while having a low solubility in water [13]. Because it dissolves in alcohol and other organic solvents, it can be used in topical treatments and sprays [14].

The effects of capsaicin include analgesia, cardioprotection, antioxidants, anti-cancer, and anti-obesity [15]. Specific binding of capsaicin to a receptor known as Transient Receptor Potential Vanilloid 1 (TRPV1) mediates some of these actions [16-18]. The molecular target TRPV1 is in charge of giving food its fiery flavor [19]. Capsaicin can activate transient receptor potential (TRP) channels, which are responsible for transmitting taste and pain [20]. Antinociceptive effects may result from desensitization of TRPV1 caused by capsaicin's excessive stimulation of TRPV1 receptors [21]. Epidemiological research have showed that chili consumption is positively connected with the protection of gastric cancer, pancreatic cancer, and lung cancer [22]. Furthermore, capsaicin has certain antagonistic effects on thyroid, liver, and esophageal cancers and can prevent the development of malignant tumors [23].

Apart from their macro and micronutrient content, different types of chilies also include a variety of bioactive chemicals with special technical and functional properties, which makes them highly advantageous from an economic standpoint [24]. Capsaicin has numerous health benefits, but too much of it can irritate the stomach and cause digestive issues [25]. In general, capsaicin is an intriguing substance from a culinary and medicinal standpoint. The objective of this review paper is to present thorough details regarding the physiological and molecular mechanisms of action of capsaicin in the body. This article also attempts to investigate the several clinical applications of capsaicin as a treatment.

History

The strong active component of cayenne peppers, capsaicin, has been used as a spicy addition for ages; some records go as far back as 7000 BC [26]. The advent of a new plaster with a high concentration that has been approved by the Food and Drug Administration (FDA) is reviving its pharmaceutical adaption, which started in the middle of the 19th century [27]. John C. Thresh gave capsaicin its current name in 1876 after it was initially isolated (in impure form) by Christian F. Bucholz in 1816. Water-insoluble

capsaicin is a homovanillic acid derivative [10]. E. K. Nelson clarified the structure of capsaicin in 1919, and Spath and Darling synthesized it in 1930 [28]. The idea of "treating like with like" or counteracting irritation has been the basis for the homeopathic use of capsaicin since its discovery to relieve searing pain. Its ability to relieve pain was first documented in the middle of the 1850s, when it was suggested that it be applied to areas of the body that were burning or itching [10]. Since the earliest reports, different capsaicin formulations have been produced to treat various chronic pain disorders.

Chemical structure

Trans-8-methyl-N-vanillyl-6-nonenamide, also known as capsaicin ($C_{18}H_{27}NO_3$), is a white, crystalline, lipophilic compound [7] (**Figure 1**). This substance is an amide that is created when caprylic acid and vanillinamine condense [15]. In ethanol, benzene, ether, and chloroform, this material dissolves readily, while it dissolves poorly in carbon disulfide [29]. Its melting and boiling points are 65 °C and 210 – 220 °C, respectively [30]. Three components make up the structure of capsaicin: an amide bond (**Figure 1(B)**), an aromatic ring (**Figure 1(A)**), and a hydrophobic side chain (**Figure 1(C)**). The main ways that the different capsaicin family members vary from capsaicin are by substitutions on the hydrophobic side chain and aromatic ring [15]. The substituents at aromatic ring positions 3 and 4 are significant active groups. For instance, the phenolic hydroxyl group at position 4 functions as an acceptor or donor of hydrogen bonds in the capsaicin agonist; capsaicin activity can be increased by substituting a hydrophobic group for this hydroxyl group [31]. Capsaicin action may be impacted by the hydrophobic side chain's type, such as an unsaturated or saturated alkyl chain, a substituted naphthyl group, or another substance.

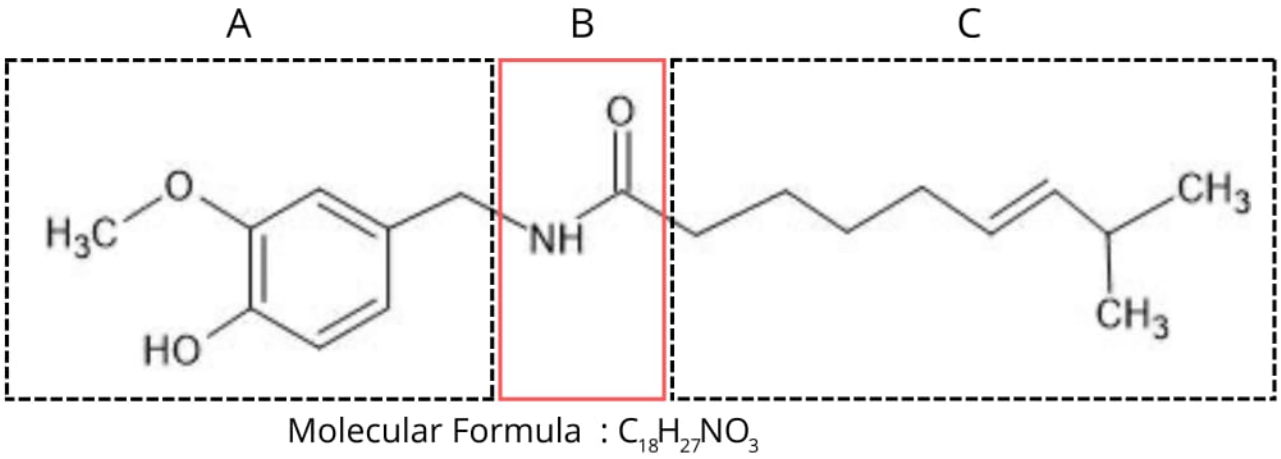

Figure 1 The capsaicin structure's functionally significant divisions are the (A) aromatic ring, (B) amide bond, and (C) hydrophobic side chain.

Mechanism of action

The past ten years have seen a significant amount of research on the mechanisms of action of capsaicin and other vanilloids. It was demonstrated about 2 decades ago that capsaicin causes afferent nociceptive neurons to produce substance P [32]. Capsaicin produces hot to burning sensations by activating afferent nociceptive neurons [33]. Its analgesic effects are mediated by substance P depletion, which makes tiny afferent sensory neurons less sensitive [34].

Capsaicin is most abundant in the placenta compared to chili fruit skin or chili seeds and this capsaicin is responsible for the spiciness of chili [35]. The "hot" sensation induced by capsaicin upon contact with human skin is primarily attributed to its interaction with the transient receptor potential vanilloid 1 (TRPV1) receptor, which is a crucial ion channel located on sensory neurons. Capsaicin, the active ingredient in chili peppers, activates TRPV1, leading to the sensation of burning pain or "heat" [36]. This receptor is responsive not only to capsaicin but also to other physical stimuli such as high temperatures (above 43 °C), protons (H^+ ions), and various lipids [37]. Upon binding to TRPV1, capsaicin induces a

cascade of events that begins with the influx of calcium ions (Ca^{2+}) into the neurons, resulting in the depolarization of the neuron's membrane and subsequent action potential generation, conveying nociceptive signals to the central nervous system [38].

Beyond the immediate sensory effects, the activation of TRPV1 by capsaicin initiates the release of proinflammatory mediators, such as substance P, from sensory neurons [39]. Substance P is well-known for its role in signaling pain and mediating inflammation [40]. The release of this neuropeptide can exacerbate the sensation of heat or burning since these mediators can further induce inflammatory responses within the skin, potentially amplifying nociceptive signals [41].

Moreover, the cellular response to capsaicin extends beyond nociceptive signaling pathways and involves the activation of keratinocytes, the predominant cells in the epidermis [42]. When activated by capsaicin, these keratinocytes can release inflammatory cytokines, such as interleukin-8. This cascade adds complexity, as these inflammatory mediators can heighten sensitization and alter neuronal excitability, thereby amplifying the pain sensation experienced during capsaicin exposure [43].

The sensation of heat or burning from capsaicin contact with the skin fundamentally arises from TRPV1 activation on sensory neurons, leading to calcium influx, action potential generation, and subsequent release of pain-inducing neuropeptides and inflammatory mediators. This multifaceted interaction underscores the intricate relationship between capsaicin, TRPV1, sensory neurons, and the skin's keratinocytes in eliciting a heightened nociceptive response.

Capsaicin and other vanilloids attach to the Transient Receptor Potential V1 receptor (formerly called the vanilloid receptor, VR1), a particular neuronal membrane receptor [44]. In addition, TRP receptors react to osmolarity, temperature, acidosis, and pain stimuli [45]. Heat (over 43 °C), protons, capsaicin, and endogenous lipid molecules called endovanilloids all cause direct and indirect activation [46]. TRPV1 is essential for both inflammatory hyperalgesia and thermal nociception [47].

The majority of TRPV1, a ligand-gated nonselective cation channel, is found on tiny fiber nociceptive neurons [48]. Calcium and sodium ion-permeable nonspecific membrane cation channels are connected to these receptors [49]. Conventional ion channel blockers do not block this channel, however arginine-rich and ruthenium-rich hexapeptides (like dynorphin) do [32]. In 1997, Caterina discovered and cloned the 838 amino acid (95 kDa) human and rodent TRPV1 receptor in mice [50]. A heat-sensitive component in this receptor mediates the burning sensation that capsaicin produces [5]. Studies on transgenic animals have demonstrated that heat hypersensitivity linked to inflammation and capsaicin sensitivity are attenuated when the TRPV1 gene is deleted [51].

The cell membrane of small fiber peripheral nociceptor neurons contains the majority of TRPV1 [52]. These receptors are found in many other tissues, including the kidneys, bladder, intestines, and brain [53]. Endovanilloid can control and activate these channels. TRPV1 is expressed on both the endoplasmic reticulum and the cell membrane [54]. The endoplasmic receptor TRPV1 controls intracellular calcium levels and is activated by endovanilloid on its own. This results in gene expression, the formation of heteromers linked to regulatory proteins, and reversible phosphorylation by phosphatases and kinases, which contribute to sensitization [55]. Synthetic TRPV1 ligands have been developed as a result of research on the TRPV1 channel and its structure-function interactions [56].

The TRPV1 receptor is activated when capsaicin binds to it at the short fiber sensory afferent nerve ends. This causes an influx of calcium and the release of inflammatory neuropeptides [34]. It limits the tolerance of capsaicin and mediates its pungent qualities [5]. Analgesia is the outcome of these neurons being functionally unresponsive to additional pain inputs after the receptors are activated [57]. Furthermore, nociceptive fiber degradation could happen [58].

Numerous substances that resemble capsaicin in structure have recently been found to be natural TRPV1 receptor agonists. These consist of anandamide (a cannabinoid), lipoxygenase metabolites of arachidonic acid, and unsaturated N-acyldopamines [59]. They are collectively referred to as endovanilloids

and all of them activate the TRPV1 receptor. Endovanilloids may be essential for maintaining capsaicin-induced receptor desensitization in inflammatory tissues by extending the analgesic impact of capsaicin in inflammatory pain conditions [60]. Hyperalgesia results from the release of endovanilloids and protons in inflammatory situations [61]. TRPV1 has been shown to be upregulated in inflammatory tissues. Ahern demonstrated that extracellular cations like Mg^{2+}, Ca^{2+}, and Na^{+} can also sensitize and activate TRPV1 [62]. Bradykinin-mediated activation of TRPV1 and heat-sensitive receptors are facilitated by physiological concentrations of these cations [63]. These voltage-activated calcium channels are dephosphorylated by capsaicin through calcium-dependent calcineurin activation [5]. This is the way capsaicin lessens the symptoms of inflammatory hyperalgesia.

Hagenacker showed that capsaicin differentiates the way it alters voltage-activated calcium channels in the rat dorsal root ganglia (DRG) [64]. Large fiber neurons in the DRG are less sensitive than small fiber neurons. The scientists hypothesize that vanilloid modifies pain signals at the spinal cord level through this function.

Studies employing resiniferatoxin, a strong capsaicin analog, indicate an other route of analgesia. Resiniferatoxin (RTX) causes the TRPV1 receptor to become activated, which raises intracellular calcium levels over time. This causes calcium-induced cytotoxicity, which kills cells that possess the TRPV1 receptor [65]. In animal models, Karai employed RTX to specifically prevent inflammatory hyperalgesia and neurogenic inflammation by deleting TRPV1-containing nociceptive neurons in single and multiple ganglia [66]. The maintenance of proprioception, high threshold mechanosensitive nociception, touch, and locomotor function are signs of selective neuronal loss. TRPV1-deficient nearby neurons are unaffected by RTX, whereas vanilloid-sensitive neurons in human dorsal root ganglion cells show a persistent increase in intracellular calcium [66]. The authors propose that deleting neurons or nociceptive nerve terminals could be a useful pain-reduction tactic.

Beyond its well-known role in nociception, capsaicin influences diverse physiological processes, as illustrated in **Figure 2**. Binding to TRPV receptors, capsaicin affects pain signaling, neuroprotection, metabolism, and antimicrobial and cardiovascular activities. Capsaicin-induced activation of TRPV1 resulting in Ca^{2+} influx can induce mitochondrial Ca^{2+} overload, leading to cytosolic activation of CytC, procaspase, AIF, and caspase pathways that promote apoptosis. Capsaicin potentially has activity I in anticancer, particularly in breast, colon, and lung cancer, through this apoptotic mechanism [67,68]. Furthermore, capsaicin-mediated alteration of gut microbiota is associated with its metabolic regulatory functions, such as activating the AMPK/PPARα pathway, increasing the secretion of GLP-1, and ameliorating glucose metabolism. These effects help the prevention of Type 2 diabetes and the management of obesity and gastrointestinal health [69,70]. Capsaicin stimulates the sympathoadrenal system, which raises metabolism [71]. Consuming capsaicin results in a dose-dependent reduction in body fat mass [72]. Studies have looked into using capsaicin to treat obesity [73]. Capsaicin mediates calpain-induced axonal terminal ablation through the neuropathic axis, leading to depolarization and decreased neuronal excitability, ultimately resulting in analgesic and neuroprotective effects [34,74]. This mechanism endows therapeutic importance in the alleviation of neuropathic pain as well as in neurodegenerative disorders, including Parkinson's and Alzheimer's disease, and even stroke prevention [75]. Additionally, capsaicin is known to have antimicrobial activity through its ability to disrupt membrane integrity in pathogens, inhibiting growth and biofilm formation in the population. Additionally, it regulates cardiovascular function through the production of calcitonin gene-related peptide (cGCRP), reducing plasma bradykinin and modulating nitric oxide (NO) pathway, which makes it a strong therapeutic candidate in hypertension and ischemic heart disease [76-78].

Capsaicin, the active compound found in chili peppers, has garnered significant attention for its potential cardiovascular benefits. Research indicates that capsaicin consumption may play a notable role in reducing risk factors associated with heart disease in adults. Notably, consistent spice consumption, particularly from chili peppers, has been linked to lower mortality rates from cardiovascular diseases in

various cohort studies across different populations [79-81].

One mechanism through which capsaicin is thought to confer cardiovascular benefits is its activation of TRPV1 channel. This activation is associated with improved endothelium-dependent vasorelaxation, which is crucial for maintaining healthy blood pressure levels and vascular function [5]. Furthermore, capsaicin appears to modulate lipid metabolism, potentially reducing the activity of phospholipid transfer protein (PLTP), a marker associated with cardiovascular disease risk. Capsaicin supplementation has been shown to improve lipid profiles in individuals with low levels of high-density lipoprotein cholesterol (HDL-C), suggesting a protective effect against coronary heart disease [82].

Epidemiological data supports these findings, where increased consumption of spicy foods correlates with a reduced risk of ischemic heart diseases, indicating that capsaicin may have a protective effect against such conditions [79-81]. Additionally, the habitual consumption of capsaicin has been associated with lower incidences of obesity and type 2 diabetes, conditions inherently linked to increased cardiovascular risk factors [83]. Moreover, capsaicin is suggested to have anti-inflammatory properties that can help mitigate the inflammatory processes often associated with cardiovascular diseases [84]. The integration of capsaicin into the diet may also encourage weight loss by enhancing the body's metabolism and promoting fat oxidation, further reducing obesity-related cardiovascular risks [85].

Additionally, concerning the acute impacts of capsaicin, there is evidence of its ability to enhance systemic blood circulation in isolated heart models, which suggests immediate cardiovascular benefits [86]. This ability to modulate coronary blood flow, combined with its systemic effects, presents a multifaceted approach in which capsaicin may contribute to cardiovascular health and decrease heart disease risk factors. Considerable evidence supports the hypothesis that capsaicin intake may significantly reduce risk factors associated with heart disease in adults through various mechanisms, including TRPV1 activation, improved lipid metabolism, anti-inflammatory effects, and promotion of metabolic health [87].

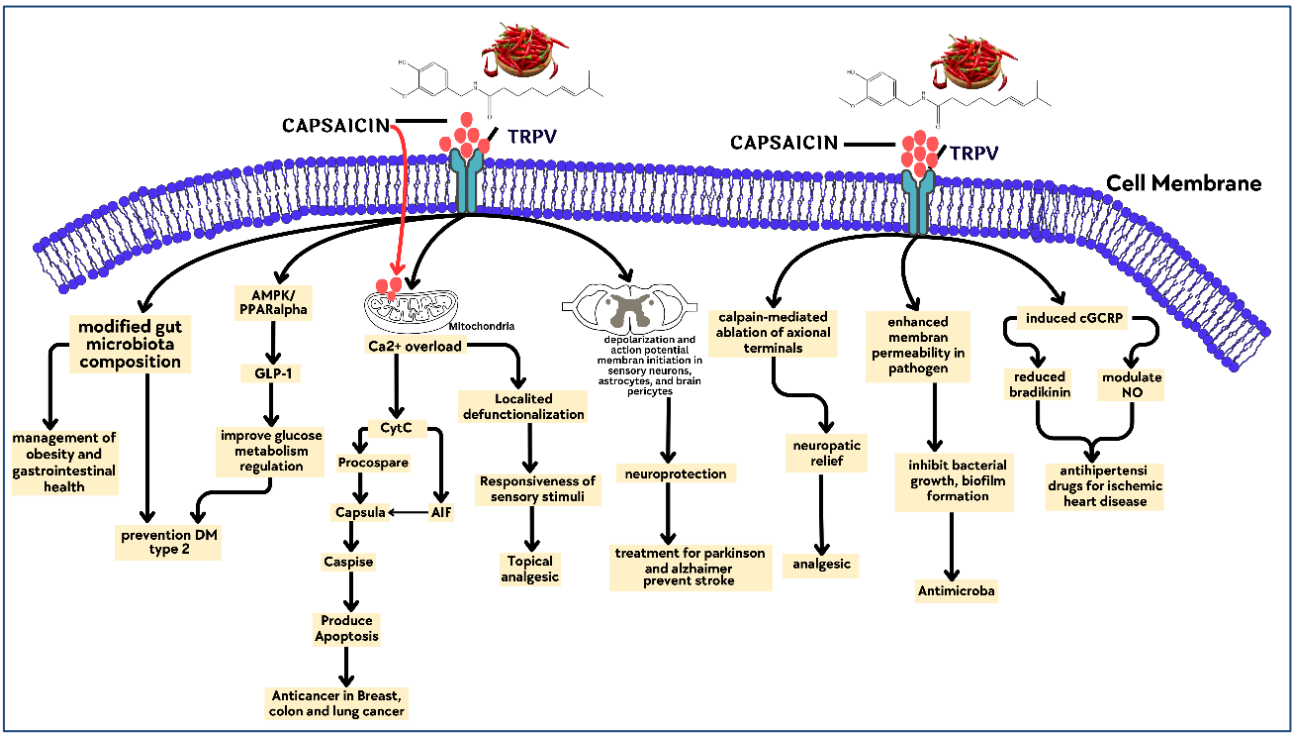

Figure 2 The role of capsaicin in modulating cellular pathways: from pain relief to anticancer, metabolism, neuroprotection, and antimicrobe.

Capsaicin's molecular mechanism of TRPV1 desensitization

To understand the relationship between substance P depletion and the subsequent desensitization, it is necessary to look at the molecular regulation of TRPV1 receptor channels. Exocytosis and antidromic responses during neuronal depolarization increase the synthesis of substance P and CGRP as a result of capsaicin-induced TRPV1 activation [88]. Substance P affects the G protein-coupled neurokinin-1 (NK-1) receptor, which colocalizes with the TRPV1 receptor on neurons that are $TRPV1^+$ [89]. TRPV1 activation through phosphorylation requires the kinase PKCe, whose translocation and activation are controlled by the NK-1 receptor [90]. Consequently, TRPV1 (hyper)sensitization (seen as hyperalgesia) and ongoing mediator release are enhanced by a positive feedback loop, which further activates $TRPV1^+$ neurons [91].

This heightened reaction results in substance P depletion, which lasts until the neuropeptide stores are depleted [10]. A complex regulatory mechanism that regulates the phosphorylation/dephosphorylation state at 2 crucial serine residues is responsible for TRPV1 activation [92]. This mechanism is dependent on a number of factors, including intracellular calcium concentration, IP3 levels, ATP, CaM kinase II, Ca-CaM binding to TRPV1, and the action of calcineurin, which inactivates TRPV1 [93]. TRPV1 inactivation is caused by loss of phosphorylation brought on by SP depletion, mainly by downregulating the PKCe pathway, which is the main regulatory mechanism for TRPV1 [52]. The balance moves toward the dephosphorylated state and TRPV1 becomes inactive (insensitive) when the activating factors are exhausted. Vanilloid administration causes a short-term downregulation of TRPV1 itself, a process known as "phenotypic switching" or defunctionalization [94]. Capsaicin's long-lasting analgesia (up to several weeks) is finally explained by a substantial decrease in the density of TRPV1-positive epidermal nerve terminals [95].

The substantial neuronal degeneration seen during extended use of capsaicin may be caused by direct neurotoxicity of capsaicin, which is reversible following drug withdrawal, and vanilloid-mediated neuronal death [96]. Reduced pain perception is correlated with the degradation of epidermal nerve fibers caused by topical capsaicin (0.075 or 8 % trans-capsaicin patch); reinnervation was reported to occur roughly 6 weeks after stopping the medication [97]. Capsaicin has a wider potential range of action than the effects resulting from TRPV1 interactions. In addition to its pharmacologic effects, capsaicin targets other chemical entities through methods that are not dependent on vanilloids [98].

Capsaicin receptor (TRPV1) importance in physiology

Capsaicin has substantial theoretical value in addition to its practical application in clinical practice as a pain and itching reliever. The physiological roles of the receptors that capsaicin acts on are revealed by this practical pharmacological tool for fundamental study [99]. New directions in the study of pain and itching have been made possible by the identification of capsaicin-sensitive receptors. It is now commonly acknowledged that TRPV1 and similar vanilloid receptors serve a number of physiological functions and are crucial relays for pain transmission, or "pain sensors" [100].

The 95 kDa protein that is the cloned TRPV1 has intracellular N- and C-terminals, and the N-terminus has 3 ankyrin domains [101]. TRPV1 is composed of 6 transmembrane domains, with the fifth and sixth transmembrane domains joined by an additional intramembrane loop [102]. Many endogenous lipid derivatives, eicosanoids, low extracellular pH, and (noxious) temperatures above 43 °C (which mediate pain hyperalgesia) can all activate TRPV1 [103]. It is now known that the brain, spinal cord, and a number of non-neuronal cells, such as platelets, vascular endothelium, immune system cells (T cells, mast cells), smooth muscle, hepatocytes, and fibroblasts, as well as epithelial cells (urothelium, enterocytes, pneumocytes, gastric epithelial cells, and keratinocytes), have lower levels of TRPV1 expression [104].

Prior research that connected TRPV1 to substance P dysregulation provided insight into the physiological function of this protein [105]. Vanilloid agonist therapy results in skin ulcers and hair loss; the damage is brought on by the depletion of substance P

from dermal nerve terminals. Alopecia areata is associated with defects in the function of vanilloid-sensitive neurons, and several recent studies have demonstrated that capsaicin can stimulate the growth of new hair [26,106]. According to a randomized controlled research, capsaicin cream works better than clobetasol in promoting the growth of vellus hair in some alopecia areata patients [107]. It has also been demonstrated that substance P promotes the growth of hair in mice [108]. TRPV1 agonists make people and animals feel pain and itching, while antagonists lessen thermal hyperalgesia by either blocking the TRPV1 receptor or interfering with the TRPV1 gene [109].

Since the TRPV1 receptor was identified as a primary target of capsaicin, extensive study has been conducted on it. As a result, there is currently broad agreement that TRPV1 is involved in pain signaling, though not just sensory processes [110]. It is now believed that TRPV1 is involved in the following physiological or pathological processes: it is important for maintaining body temperature, controlling feeding and weight, reducing inflammation, and preventing respiratory diseases [111]. Interestingly, agonists that activate TRPV1 have positive effects on gastrointestinal and cardiovascular health [17].

Recently discovered endogenous ligands for TRPV1 may suggest that capsaicin's therapeutic effect is dependent on competition with different endogenous [5]. TRPV1 is strongly stimulated by lipoxygenase products and derivatives of arachidonic acid (such as arachidonic-ethanolamide, anandamide, which was formerly a cannabinoid receptor 1 agonist, N-arachidonoyl dopamine, and N-oleoyl dopamine) [112].

Analogs of capsaicin

The typical burning and stinging sensation that topical capsaicin produces is initially intense and disagreeable (irritating), and it has a relatively low therapeutic index [113]. Capsaicin can soon become unfeasible to use due to its poor tolerance, which can result in significant withdrawal rates (up to 30 %) during therapy [114]. Consequently, a number of analogues, both TRPV1 agonists and antagonists, are being investigated and assessed as safer and better-tolerated substitutes. Resiniferatoxin (RTX), which was initially identified in 1975 and subsequently reported as a very potent vanilloid, is a better TRPV1 agonist [115]. RTX was found to have a superior desensitization to irritation ratio than capsaicin in animal experiments. Capsaicin is less effective than RTX at causing nerve desensitization [116].

The Chinese herbal remedy Wu-Chu-Yu contains rutaecarpine, a significant quinazolinocarboline alkaloid that has long been used in traditional Chinese medicine to treat postpartum bleeding, headaches, amenorrhea, and gastrointestinal issues [117]. It appears that released neurotransmitters such substance P and CGRP influence the different pharmacological activities of rutaecarpine via activating TRPV1 [118]. Capsazepine, a TRPV1 antagonist that has been shown to be effective in animal models of pain and inflammation, was assessed as an additional possible substitute for capsaicin [119]. Numerous artificial TRPV1 agonists and antagonists have recently been investigated and assessed.

Pharmacokinetics

The skin absorbs topical capsaicin well. Topically applied capsaicin quickly reaches the highest concentration in the skin [120]. Preparations including isopropyl have a higher concentration than those with propylene glycol or mineral oil. Capsaicin has a half-life of roughly 24 h. Topical administration of a 3 % capsaicin solution (consisting of 35 % hydrocapsaicin, 55 % capsaicin, and 10 % other analogues) using 3 distinct vehicle preparations (70 % isopropyl alcohol, propylene glycol with 20 % alcohol, and mineral oil) was assessed in a study involving 12 participants [121]. Capsaicinoids were detected in the stratum corneum within a min of injection, and a steady state was quickly reached. Subjects receiving the 70 % isopropyl alcohol preparation had maximum concentrations that were nearly 3 times higher than those getting the mineral oil and propylene glycol preparations [121]. This suggests that capsaicinoids are more soluble in bigger amounts of alcohol. All 3 formulations had a half-life of roughly 24 h for capsaicin.

Following intravenous injection, capsaicin was extensively dispersed throughout the rats' brain, spinal cord, and liver [122]. Cytochrome p450 enzymes convert capsaicinoids into alkyl dehydrogenated, macrocyclic, omega-, and omega-1 hydroxylated compounds [123]. The primary metabolite of capsaicin

is dihydrocapsaicin. The kidneys eliminate dihydrocapsaicin and its byproducts [124]. The kidneys also eliminate capsaicin. Currently, topical creams containing 0.025 and 0.075 % capsaicin are available [125]. Application to the afflicted area 2 to 4 times per day is the suggested dosage. There are presently no parenteral doses of capsaicin available. Although adenosine inhibits capsaicin's binding to its receptor, it is unclear what the therapeutic implications of this interaction are [126]. The mucosal vasodilation that capsaicin produces may change how well other medications that are applied topically or taken orally are absorbed [5]. But it doesn't obstruct the flow of electrolytes and water via the jejunal mucosa.

Adverse effects

Applying capsaicin topically causes burning and irritation [127]. In comparison to 15 % of patients who took a placebo, over 54 % of patients who took capsaicin reported experiencing one or more local side effects [128]. This corresponds to the 2.5 number needed to cause harm (NNH). The number needed to cause harm is close to 10 if stopping active therapy is taken as a measure. One of the main drawbacks of using capsaicin as a topical treatment is that topical local anesthetics cannot consistently stop the searing side effect of capsaicin [129].

Another adverse effect, cough, was experienced by 8 % of individuals who used the 0.075 % cream, but not by those who used the 0.025 % cream [130]. Capsaicin has been used extensively in cough tests because it produces a dose-dependent and consistent cough response [131]. The mechanism behind the cough reflex is significantly influenced by TRPV1 receptors on sensory airway neurons [132]. According to 1 study, asthmatics were more sensitive to capsaicin in terms of coughing and bronchoconstriction, which suggests that asthmatic participants had higher TRPV1 activity [133]. This is in line with the discovery that asthmatic patients' airways have higher levels of endovanilloid [134].

Capsaicin-based sprays are employed as self-defense and riot control tools [135]. In this situation, capsaicin is a very irritating chemical that makes the skin burn or sting [127]. Exposure of the eyes results in blepharospasm, conjunctivitis, discomfort, and excessive weeping [136]. It can result in scorching diarrhea, nausea, vomiting, and stomach pain if used in excess [137].

Capsaicin, the active component in chili peppers, has a complex relationship with the gastrointestinal (GI) system, including its effects on the stomach and its potential to induce diarrhea. While capsaicin is often praised for its health benefits, including weight loss and metabolic enhancement, its pungent nature also presents irritant qualities that can elicit a range of physiological effects in the digestive tract [138].

Capsaicin influences stomach function primarily through its action on capsaicin-sensitive afferent neurons, which play a crucial role in regulating gastric motility and acid secretion. Studies indicate that capsaicin can promote gastric emptying, thereby affecting how substances are processed in the stomach and subsequently in the duodenum [139,140]. The study by Sumano-Lopez *et al.* [139] suggests that capsaicin may enhance the absorption of certain medications by increasing blood flow in the intestinal pilli, potentially due to its irritant effects. This property underscores capsaicin's dual role as a digestive stimulant and an irritant.

Furthermore, capsaicin has been linked to protecting the gastric mucosa at low doses, while high concentrations may induce gastric irritation, cramps, and ulcers [141,142]. Research indicates that ingested capsaicin can lead to increased discomfort within the gastrointestinal system, demonstrating that varying doses have divergent effects on gut health [143]. Notably, high doses of capsaicin trigger a rapid increase in gastric motility, which could lead to symptoms such as diarrhea in some individuals, especially those with sensitive constitutions or pre-existing GI conditions like irritable bowel syndrome (IBS) [144].

In addition to its irritative effect, capsaicin interacts with the gut microbiota, which plays a crucial role in digestive health. The study by Zhang *et al.* [145] highlights how dietary capsaicin can complicate gut dysbiosis, potentially leading to gastrointestinal distress, which could include diarrhea as a symptom. Moreover, capsaicin's effect on the autonomic nervous system can alter gastrointestinal motility, increasing the likelihood of faster transit and consequent diarrhea in sensitive individuals [146].

While capsaicin can have beneficial effects on appetite and metabolic parameters, its irritant properties at higher concentrations can lead to adverse effects on the digestive system, including gastric discomfort and diarrhea. Individual reactions to capsaicin can vary significantly, suggesting a need for caution, particularly for those with a history of gastrointestinal issues [147,148]. Thus, its overall impact on the stomach and potential to cause diarrhea is dependent on the dose and the individual's sensitivity to spicy compounds.

Clinical use

There are several different clinical problems for which capsaicin has been employed.

Analgesic

The transient release potential ion channel family includes the heat-sensing Ca^{2+}-selective TRPV1 member [44]. It has also been demonstrated that neuropathic pain is mediated by TRPV1 in the prelimbic and infralimbic brain [149]. TRPV1 is extensively found in the liver, glial cells, brain tissue, bladder, kidney, gut, mast cells, macrophages, polymorphonuclear granulocytes, and epidermal keratinocytes [16].

One TRPV1 agonist that lowers the activation threshold is capsaicin [150]. It's special because once capsaicin activates TRPV1, the receptor goes into a persistent refractory state where it is insensitive to pain, inflammation, and mechanical stress [5]. This so-called "defunctionalization" happens when the channel pore closes as a result of a conformational shift that is reliant on extracellular Ca^{2+} [151]. It is yet unknown how much of the apparent analgesic benefits of capsaicin can be explained by this transient "defunctionalization".

TRPV1 mediates Ca^{2+} inflow and glutamate release when activated by capsaicin, which can harm sensory nerve endings and cutaneous autonomic nerve fibers, impairing pain perception [33]. The capsaicin analog resiniferatoxin reduces the experience of heat discomfort in adult mice by destroying unmyelinated nerve fibers expressing TRPV1 and damaging myelinated nerve fibers expressing TRPV1 [34].

Antioxidant

Human low-density lipoprotein peroxidation can be blocked by capsaicin, which has also been demonstrated to reduce lipid peroxidation in rat liver and mitochondria, as well as in red blood cell membranes [152]. In some instances, capsaicin's antioxidant activity actually surpasses that of vitamin E [153,154]. Because capsaicin inhibitors stop reactive oxygen species from oxidizing glutathione, they can reduce oxidative stress and boost antioxidant capacity in cells [155]. Capsaicin can reverse the propensity for high blood cholesterol levels to inhibit the antioxidant enzymes glutathione reductase, glutathione transferase, and superoxide dismutase [156]. Additionally, capsaicin can eliminate free radicals such 1,1'-diphenyl-2-picrylhydrazyl (DPPH) [124]. Other members of the capsaicin family, such as dihydrocapsaicin and 9-hydroxycapsaicin, seem to have antioxidant properties comparable to those of capsaicin [157].

The antioxidant activity of capsaicin and other members of the family seems to be dependent on the benzene ring and its substituents. The antioxidant activity can be greatly affected by the methoxy and hydroxy substituents in the ortho position of the benzene ring, whereas the benzene ring of capsaicin can interact with the benzene ring of DPPH [158]. All secondary metabolite groups from plants, including flavonoids and phenolics, have an antioxidant action comparable to that of the alkaloid group of metabolite chemicals [159,160]. Serum lipoprotein oxidation levels were decreased in adults who took capsaicin for 4 weeks [161]. Capsaicin can lower oxidative stress in mitochondria, including lipid peroxidation. It can lessen myocardial and renal ischemia-reperfusion damage. TRPV1 appears to be the mediator of the majority of these antioxidant actions [15]. Stronger antioxidant action in capsaicin analogues is still being sought after.

Cardioprotective

TRPV1 is expressed in vascular endothelial cells, sensory neurons, and cardiovascular tissues close to the epicardium [17]. Free oxygen radicals produced when the heart's blood flow is reduced, as happens during a myocardial infarction, activate TRPV1 [162]. TRPV1-binding 12-hydroperoxyeicosatetraenoic acid, a

product of arachidonic acid 12-lipooxygenase, is also elevated in myocardial damage [163]. There may be cardioprotective benefits to receptor activation, which could reduce ischemic/reperfusion injury and infarct size [164].

In blood arteries, TRPV1 can either promote vasodilation or vasoconstriction, depending on the circumstance [44]. Substance P is released when TRPV1 is activated in vasoconstriction, and it binds to neurokinin 1 [165]. Nitric oxide synthase and calcitonin gene-related peptide or protein kinase A are released when TRPV1 is activated in vasodilation. TRPV1 activation raises intracellular Ca^{2+} in both situations [166].

Capsaicin may alter the fluidity of platelet membranes, hence preventing platelet aggregation [167]. Since competing TRPV1 inhibitors do not block the impact, this mechanism seems to be independent of TRPV1 [168]. However, it has also been demonstrated that capsaicin increases platelet aggregation via a process that is dependent on TRPV1 [4]. Through this mechanism, TRPV1 can stimulate serotonin release to support platelet activity in response to thrombin and adenosine diphosphate [169].

Anti-cancer

Among the many pharmacological characteristics of capsaicin are its antigenotoxic, antimutagenic, and anticarcinogenic actions. Nonetheless, contradictory research points to capsaicin's possible function as a carcinogen, mutagen, and tumor promoter, referring to it as a "double-edged sword". Numerous possible investigations of capsaicin's carcinogenic effects *in vivo* have been documented. For instance, Chanda *et al.* [170] used the Tg.AC transgenic mouse model to assess the dermal carcinogenic potential of capsaicin. Their findings showed that animals co-treated with tetradecanoylphorbol-13 acetate (TPA) developed numerous dermal mass growths. Additionally, Liu *et al.* [171] discovered that by upregulating the expression of tumor-associated NADH oxidase (tNOX), low concentrations of capsaicin (0.1 – 10 μM) can stimulate tumor cell proliferation and migration in HCT116 cells. Moreover, mice used in in-vivo studies showed that capsaicin encourages the growth of gastrointestinal malignancies in these animals. Capsaicin can speed up the formation of cancer cells, particularly colorectal and hepatocellular carcinoma, in people who like spicy meals, according to extensive case-control studies.

Even while pro-oncogenic effects are described in a lot of literature, there is still disagreement over how to use this research, and further studies are required to confirm the results. However, because capsaicin had no effect on the development of carcinogenesis in a mouse model of preneoplastic colon cancer, it was determined that it was safe to ingest in large quantities [172]. It is commonly known that capsaicin and other medications work together to prevent cancer. Inducing apoptosis, capsaicin and resveratrol increase nitric oxide (NO) in a p53-dependent way [173]. AMP-activated protein kinase (AMPK) and cyclooxygenase 2 in breast cancer cells were altered when the dietary phytoestrogen genistein and capsaicin were combined, exhibiting synergistic anticancer action [174]. According to Clark *et al.* [175], capsaicin and 3,3′ diindolylmethane, a significant in-vivo metabolite of indole-3 carbinol found in many cruciferous vegetables, help induce apoptosis in colorectal cancer by changing the transcriptional activity of nuclear factor kappa B, p53, and target genes regulating apoptosis.

Capsaicin impacts the viability of cancer stem cells by blocking the Notch signaling pathway in breast cancer stem cells [176]. Cell proliferation is a critical marker for cancer prevention and is recognized to play a major role in multistage carcinogenesis. It has been demonstrated that dihydrocapsaicin and capsaicin suppress the growth of a range of non-growth or malignant cell lines by reducing cellular metabolic activation, causing cycle arrest, and inducing apoptosis [177]. These findings suggest that both receptor-independent direct and receptor-dependent indirect pathways are involved in the cellular death that capsaicin or dihydrocapsaicin causes. Capsaicin interacts with caspases, particularly caspases 1 and 3, to directly induce apoptosis [178]. On the other hand, the indirect pathway necessitates that capsaicin interact with TRPV-1, which raises intracellular calcium and triggers the emergence of early and late apoptotic indicators [179]. In summary, capsaicin significantly reduces the spread of cancer by altering the expression levels of genes and enzymes that are involved in the growth, cell cycle arrest, signal transduction, apoptosis, and metastasis of cancer cells. Capsaicin's alkaloid

status contributes to this mechanism as well, much like the potential of other secondary metabolites derived from the phenolic and flavonoid groups [180,181].

Anti-obesity

Tools and methods for reducing and maintaining weight are receiving a lot of attention globally because of the serious threat to public health posed by the notable rise in obesity over the past ten years. Obesity is often the result of an imbalance between excessive energy intake and insufficient energy expenditure. This imbalance can lead to many metabolic problems, such as diabetes, insulin resistance, fatty liver disease, and cardiovascular disease [182]. Evidence strongly suggests that capsaicin has anti-obesity properties [183,184].

Capsaicin is a prominent tactic that has been shown to suppress adipogenesis and promote lipid oxidation in adipocytes [78]. It prevents weight gain by increasing uncoupling protein 2 (UCP2) and uncoupling protein 3 (UCP3), reduces hunger by influencing ghrelin, promotes thermogenesis, regulates hypothalamic satiety, and maintains metabolic balance by influencing gut flora [185]. Capsaicin suppresses preadipocyte differentiation, proliferation, and lipogenesis by upregulating PPARα, UCP2, and adiponectin in 3T3-L1 adipocytes and downregulating CCAAT/enhancer binding protein (C/EBPα), leptin, and peroxisome proliferator-activated receptor γ (PPARγ) [186]. Capsaicin increases intracellular Ca^{2+} levels, sirtuin-1 expression, and TRPV1 channels, which causes adipose tissue browning and prevents mice from becoming obese from a high-fat diet [187].

Capsaicin, the active component found in chili peppers, has been widely studied for its potential role in enhancing caloric expenditure and assisting in anti-obesity strategies. A comprehensive understanding of its mechanisms reveals that capsaicin can stimulate energy metabolism, primarily through the activation of the TRPV1 channels, which subsequently leads to increased thermogenesis and lipid oxidation [4]. When capsaicin is consumed, it triggers a series of physiological responses, including the enhancement of catecholamine release from the adrenal medulla [5]. This has been associated with increased lipolysis and fat oxidation which can facilitate weight management.

Clinical studies provide compelling evidence for the relationship between capsaicin and enhanced calorie burning. For example, a systematic review highlighted that capsaicin significantly increases energy expenditure and promotes fatty acid oxidation, indicating its effectiveness as a dietary inclusion for individuals seeking to manage their weight [73]. Specifically, capsaicin-rich meals resulted in a measurable increase in metabolic rate, further supporting its potential utility in combating obesity [188]. Additionally, Janssens *et al.* [189] demonstrated that capsaicin consumption leads to acute effects on energy expenditure even in the context of a negative energy balance, pointing to its powerful stimulatory effects on metabolism.

Furthermore, recent insights have explored the chronic adaptations associated with capsaicin intake. Longitudinal studies have indicated that prolonged capsaicin ingestion can sustain an increased rate of fat oxidation during weight maintenance phases [190]. While the immediate effects are well-documented, questions remain regarding the long-term weight-regulating impact of capsaicin supplementation post-weight loss; some studies reported no significant effects on weight regain while still observing heightened thermogenesis and fat oxidation across 3 months [191].

In addition to thermogenic responses, capsaicin appears to exert anti-obesity effects through mechanisms related to inflammation reduction. Yang *et al.* [192] emphasize that capsaicin has the potential to mitigate chronic low-grade inflammation, a common pathway associated with obesity [192]. The ability of capsaicin to modulate inflammatory responses and promote energy expenditure could yield significant benefits in the fight against obesity and associated metabolic disorders [193].

The interplay between capsaicin and increased calorie burning is tied to its activation of TRPV1 channels, leading to elevated thermogenesis and lipid metabolism, exhibiting a multifaceted approach for obesity management [194]. This makes capsaicin a compelling candidate for further research in dietary interventions aimed at weight control.

In another animal study with obese diabetic rats, capsaicin prevented the rise in blood glucose and insulin levels, changed the composition of the gut

microbiota, and increased plasma and ileal levels of glucagon-like peptide-1 (GLP-1) [195]. Joo *et al.* [196] used a specific proteomic technique to examine protein changes caused by capsaicin treatment in mice's white adipose tissue (WAT). They showed that after capsaicin treatment (10 mg/kg) in WAT, protein-related thermogenesis and lipid metabolism were altered, leading to an 8 % decrease in body fat. This helped to clarify how capsaicin fights obesity at the molecular level. Furthermore, peroxiredoxin, vimentin, and NAD(P)H: quinone oxidoreductase 1 (NQO1) levels were found to be significantly reduced (> 2-fold) following capsaicin administration, despite an increase in flavoproteins and aldo-keto reductases. Given the notable changes in proteins associated with thermogenesis and lipid metabolism after capsaicin therapy, it is clear that capsaicin plays a crucial role in the regulation of energy metabolism [197].

Gastroprotective

Widely dispersed throughout the gastrointestinal tract, capsaicin-sensitive sensory nerves are thought to be crucial for preserving the integrity of the gastrointestinal mucosa and shielding it from harmful stimuli [198]. Additionally, in numerous animal models of gastrointestinal mucosal damage brought on by chemicals like ammonia, ethanol, aspirin, hydrochloric acid, or indomethacin, capsaicinoids have shown gastroprotective qualities [199]. Capsaicinoids can have a wide range of effects on the gastrointestinal mucosa, with both beneficial and detrimental effects contingent on the dosage and length of medication use. Excessive dosages of capsaicinoids can harm sensory nerves that are sensitive to capsaicin and deplete neurotransmitters, which may have detrimental effects on the digestive system [4]. On the other hand, lesser dosages can promote gastric mucus secretion, enhance basal blood flow to the stomach mucosa, and hasten the recovery of gastric epithelial tissue—all of which help to safeguard and defend the gastrointestinal tract [200]. Despite having limited clinical uses, capsaicin is frequently used in research on gastrointestinal physiology, pathology, and pharmacology due to its dual effects on sensory neurons, which can cause them to become sensitive or desensitized [5].

Dermatoprotective

TRPV1 is expressed in keratinocytes in humans [201]. In psoriatic epidermis, capsaicin inhibits hypoxia-inducible factor-1α, which slows epidermal proliferation even while epidermal TRPV1 activation causes the production of inflammatory factors [202]. It also lowers irritation mediated by histamine, proteinase-activated receptor-2, and substance P [15]. However, prior research did not find any beneficial effects of capsaicin on notalgia paresthetica, refractory idiopathic pruritus, or pruritus brought on by hemodialysis [203]. An animal study found that capsaicin was actually associated with the development of chronic relapsing pruritic dermatitis, which was linked to an increase in mast cell numbers and hyperproduction of immunoglobulin E [204].

Antimicrobial

The antimicrobial qualities of capsaicin have been recognized for millennia [205]. According to historical records, cayenne pepper extracts, both hot and cold, have been used to treat a number of illnesses and have been demonstrated to be effective against bacteria like *Clostridium sporogenes*, *Bacillus cereus*, *Streptococcus pyogenes*, *Bacillus subtilis*, and *Clostridium tetani* [206]. Capsicum fruit's alcohol has potent antifungal and antibacterial effects on both Gram-positive and Gram-negative bacteria [207]. The microorganisms die as a result of capsaicin's damage of their membranes [208].

Anti-inflammatory

The capsaicinoid that has generated the most study attention is capsaicin, which relieves pain. Since of its anti-inflammatory qualities, capsaicin is frequently used in topical gels and patches to reduce pain, even though it can promote inflammation since it stimulates nerves [209]. The anti-inflammatory properties of capsaicin are also known to be linked to the production of pro-inflammatory mediators and the activation of TRPV1 channels [51]. Numerous substances and components, including uncomfortable heat, protons, and vanilloids, can activate TRPV1, a non-selective cation channel [210]. Research that uses RNA interference to "knock out" TRPV1 or delete the TRPV1 gene has demonstrated that TRPV1 is crucial for pain perception [211].

TRPV1 antagonists provide a new paradigm in pain management since it is anticipated that they may reduce pain perception by inhibiting unwanted endogenous substances that stimulate TRPV1 [212]. In contrast to other natural irritants, capsaicinoids, such dihydrocapsaicin or capsaicin, first activate sensory neurons and then cause desensitization, a protracted refractory condition [213]. Capsaicin also releases endogenous somatostatin, which shields the retina from ischemia and reperfusion-induced damage, according to recent research on anti-inflammatory medications [214].

Anti-neurodegenerative

Several animal models of Alzheimer's disease (AD) have demonstrated the promise for capsaicin as a treatment [215]. Capsaicin can partially prevent the biochemical and behavioral changes that resemble AD that are caused by streptozotocin [216]. Capsaicin inhibited the production of amyloid fibrils from amyloid precursor protein in the APP/PS1 animal model. In a third model of AD, capsaicin significantly reduces tau hyperphosphorylation and synaptic damage brought on by cold water stress [216]. The therapeutic potential of capsaicin in foods to treat and maybe prevent AD should be investigated further. Based on lipopolysaccharide-induced inflammation in an animal model of Parkinson's disease, capsaicin appears to activate TRPV1 in M1/M2 dopaminergic neurons, which may lessen neuroinflammation and oxidative stress of activated glia [217]. This study used suitable antagonists to confirm the positive effects of capsaicin and TRPV1. Capsaicin's potential for treating Parkinson's disease should be investigated further, and the mechanisms underlying it should be clarified.

Meta-analysis on capsaicin

Capsaicin, the active component of chili peppers, has garnered attention in medical research for its multifaceted effects in various health conditions. A body of evidence suggests its potential benefits, particularly concerning pain management, weight loss, and cancer prevention. Several meta-analyses have been conducted to evaluate these impacts systematically.

One major area of interest is the use of capsaicin in the management of pain. A study by Yong *et al.* [218] highlighted the efficacy of topical capsaicin for treating postherpetic neuralgia, demonstrating significant pain relief and good tolerability among patients. This is supported by findings from a systematic review by Mason *et al.* [219] which confirmed capsaicin's effectiveness for chronic pain management related to neuropathic and musculoskeletal disorders. Furthermore, research indicates that capsaicin patches can significantly alleviate symptoms of diabetic peripheral neuropathy, as shown in a narrative systematic review that found 8 % capsaicin patches to reduce symptoms effectively [220].

Additionally, the weight management potential of capsaicin has been examined in various studies. Zhang *et al.* [221] conducted a meta-analysis revealing that capsaicin supplementation may yield modest reductions in body mass index (BMI) and waist circumference among overweight and obese individuals. Similarly, Zsiboras *et al.* [197] explored the effects of capsaicin on energy metabolism and fat oxidation, emphasizing its potential role in obesity management, although results remain somewhat controversial across different studies [197]. Research has suggested that capsaicin intake might stimulate metabolic processes, contributing to weight loss through thermogenesis and appetite regulation [188].

Beyond pain relief and weight management, capsaicin's role in cancer prevention has also been documented. Pabalan *et al.* [222] analyzed the impact of capsaicin intake on the risk of gastric cancers, suggesting that moderate consumption could offer protective benefits. This perspective is reinforced by findings from Mosqueda-Solis *et al.* [223], which reported that capsaicin has chemopreventive properties in oral cancers by promoting apoptosis and inhibiting malignant cell proliferation [223].

Evidence from various systematic reviews and meta-analyses suggests that capsaicin has significant therapeutic potential across multiple health domains, including pain management, obesity treatment, and cancer prevention. Its multifaceted efficacy, while still requiring further study particularly in human populations, indicates that capsaicin could serve as a valuable addition to clinical practices.

Conclusions

A substance called capsaicin, which is present in capsicum, has a number of intriguing medicinal uses. In addition to giving food a fiery taste, capsaicin has been shown to improve heart health, speed up metabolism, and reduce discomfort. It has also been demonstrated in numerous studies to increase calorie burning, which can help with weight loss. Specific binding of capsaicin to a receptor known as Transient Receptor Potential Vanilloid 1 (TRPV1) mediates some of these actions. The molecular target TRPV1 is in charge of giving food its fiery flavor. Nevertheless, despite its many advantages, capsaicin should be used carefully, particularly by people with sensitive skin or digestive issues. All things considered, capsaicin is a substance that may offer numerous health advantages, but it's crucial to use it sensibly and pay attention to the recommended dosage.

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Declaration of Generative AI in Scientific Writing

The authors declare that no generative AI tools were used in the writing or preparation of this manuscript.

CRediT author statement

MS, ARK, MHE, and IM drafted the manuscript. BWKW, ATK, SAS, and BPP revised and edited the manuscripts. AOA, PS, SPM, and RZA participated in the preparation and critical checking of the manuscript. IFM, AA, HP, and ML edited the references. All authors read and approved the final manuscript draft.

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