Research Article

REPURPOSING CAPSAICIN AS A POTENTIAL TREATMENT FOR SKIN CANCERS: A COMPREHENSIVE REVIEW

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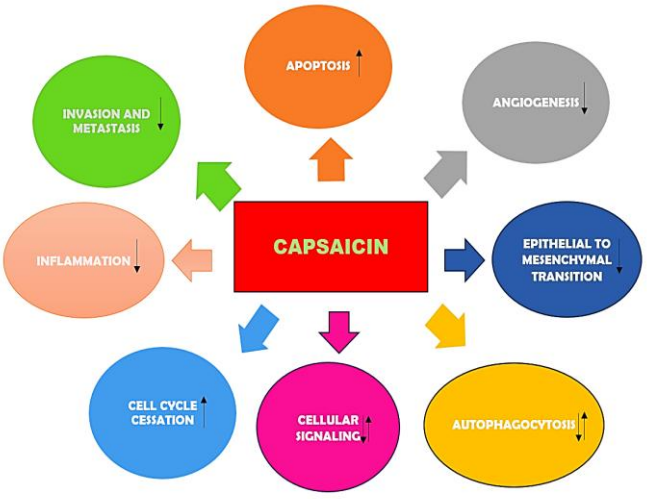
Abstract

Skin cancer, encompassing melanoma, squamous cell carcinoma, and basal cell carcinoma has witnessed a remarkable surge in incidence over recent decades, necessitating novel and effective therapeutic interventions. Although surgery is still the most common form of therapy, new therapeutic approaches are being investigated in an effort to enhance results and lessen side effects. Natural compounds have received a great deal of attention for their varied pharmacological qualities in response to this growing global health problem. Among these, the alkaloid capsaicin, which is found in large quantities in chilli peppers, has drawn a lot of attention due to its stated ability to prevent cancer. In-depth investigation of capsaicin's potential as a skin cancer therapy is the goal of this thorough analysis. Research is done on the preclinical results, possible therapeutic uses, and mechanisms of action of the chemical. In addition, the study highlights obstacles and prospective avenues for using capsaicin's medicinal benefits. This review, which provides a thorough examination, provides important new information about capsaicin's potential to combat skin cancer.

Keywords: Capsaicin, skin cancer, basal cell carcinoma, squamous cell carcinoma, melanoma

Graphical Abstract - An overview of capsaicin's anticancer initiatives in skin cancer



1. Introduction

Skin cancer is an imminent global health concern due to increased occurrence in recent decades. It is one of the most common types of malignancy, with an estimated one in three cases detected globally [1]. UV radiation from tanning beds, natural sunshine is the main cause of skin cancer growth [2]. The skin, the biggest organ in the body, is vulnerable to carcinogenic insults because it acts as a vital barrier against environmental aggressors, UV radiation [3]. Basal cell carcinoma (BCC), Squamous cell carcinoma (SCC), and melanoma are the most prevalent types of skin cancer though Non-melanoma skin cancers (NMSCs) account for most instances of skin cancer worldwide [4]. Their high incidence rates and propensity for local tissue damage make them a target for timely and efficient treatment options, though they develop slowly and have a lesser metastatic potential than melanoma, the most deadliest type of skin cancer [5,6].

The three mainstays of conventional skin cancer treatment are surgery, radiation therapy, and chemotherapy. The gold standard for localised skin malignancies is surgical excision, which is frequently combined with Mohs micrographic surgery for exact tumour removal [7] along with major functional and cosmetic impairments if the tumour is deeply infiltrating tumours especially in sensitive locations [8]. An alternative treatment is radiation therapy, which uses focused radiation beams to destroy tumour cells [9] whereas several variables such as tumour depth, histological subtype may restrict its effectiveness [10]. Chemotherapy has shown poor efficacy in skin cancer therapy due to resistance mechanisms, off-target effects, and systemic toxicity [4] and also negatively affect healthy normal cells, with side effects such as tiredness, nausea, and myelosuppression [11].

There is an overwhelming desire to investigate complementary and alternative methods for managing skin cancer. Capsaicin, a naturally occurring substance produced from chilli peppers (Capsicum spp.), has attracted a lot of research due to it's capacity to regulate angiogenesis, apoptosis, proliferation, and inflammation, across different forms of cancer [12]. Furthermore, the well-established safety profile of capsaicin, especially when used topically, offers an enticing path for therapeutic research.

Capsaicin: chemistry, sources, and pharmacokinetics

The predominant bioactive component of chilli peppers (*Capsicum spp*.) is capsaicin, an alkaloid molecule with an amide bond, a hydrophobic alkyl chain, a vanillyl group with a molecular weight of around 305.4 Da, with the formula C18H27NO3 [11,13]. The burning sensation and distinctively strong flavour are caused by the vanillyl group. This feeling results from the transient receptor potential vanilloid 1 (TRPV1) ion channel, which is mostly expressed in sensory nerve fibres [12,14]. The main source of capsaicin is chilli peppers, albeit the amount of the compound varies depending on the kind and section of the pepper and the concentration ranges from a few thousand to over a million Scoville Heat Units (SHU) and the spiciness comes from the seeds and pith [13,14].
The Absorption, Distribution, Metabolism, and Excretion (ADME) pathways regulate the fate of capsaicin within the body:
Absorption: Capsaicin accumulates primarily through the skin when applied topically or through the gastrointestinal tract when administered orally. Since capsaicin is lipophilic, it may penetrate through cell membranes more easily during passive diffusion, in comparison to intestinal absorption as the particular kind of vehicle chosen affects topical absorption [15,13].

Distribution: Following absorption, capsaicin travels throughout the body via the bloodstream. Its ability to penetrate the blood-brain barrier may also play a role in how it affects the central nervous system [15,13].

Metabolism: A significant amount of capsaicin's metabolism occurs in the liver. The primary metabolic route is mediated by the enzyme cytochrome P450 2E1 (CYP2E1), which catalyses the hydroxylation of capsaicin to produce a variety of metabolites, including 8-methyl-nonanoic acid and vanillyl amine [13,16].

Excretion: The main method of excreting capsaicin metabolites is urine; however some biliary excretion occurs as well. Individual differences in metabolic rate and genetic variances in enzyme activity affect the elimination half-life of capsaicin and its metabolites [16,18].

A number of variables affects capsaicin's bioavailability, the percentage of a given dosage that enters the systemic circulation. Dietary lipids improve the absorption of capsaicin and also nanoencapsulation is to enhance bioavailability for medicinal purpose. [16, 17,18,19].

Molecular mechanisms of capsaicin in cancer therapy

Capsaicin found in chilli peppers, has potential as a therapy for skin cancer due to anti-cancer mechanisms such as -
Activation of TRPV1 Receptors: The primary mechanism is the activation of Transient Receptor Potential Vanilloid 1 (TRPV1) receptors. A calcium ion (Ca2+) surge is caused by capsaicin binding to TRPV1 receptors(Fig1.), which in turn causes subsequent cellular reactions [19]. Neurotransmitters including substance P, which can alter cellular reactions and tumour behaviour, are also released as a result of this activation [20].
Induction of Cell Cycle Arrest and Apoptosis: An important mechanism of planned cell death where the intrinsic mitochondrial route and the extrinsic pathway are targeted by Capsaicin. Capsaicin effectively suppresses the

transcriptional activity of β-catenin in colorectal cancer cells, [21], triggers apoptosis(Fig1.) in gastric cancer cells through regulation of MAPK signaling pathways and inhibits cell migration by down-regulating MMP-9 via the AMPK pathway in cholangiocarcinoma cells [22, 23].

Anti-Proliferative Effects: In several cancer cell lines, including skin cancer, capsaicin has strong anti-proliferative effects (Fig1.). According to studies, capsaicin slows down cell division and impedes the development of tumours by inhibiting the production of proliferative markers downregulating cyclin-dependent kinases (CDKs)[24,25,26].

Inhibition of Angiogenesis: Capsaicin is acknowledged to possess an intense inhibitory influence on angiogenesis as evidenced by both in vitro and in vivo studies, suggesting that it is a powerful anti-angiogenic drug [27]. Xu et al. (2018) noticed capsaicin limits metastasis by altering the TRPV1 channel in a study that was concentrated on human papillary thyroid cancer BCPAP cells [28].

Modulation of Inflammatory Responses: The onset and spread of skin cancer are significantly influenced by chronic inflammation. By preventing the activation of NF-κB, a transcription factor important in inflammation, capsaicin has anti-inflammatory actions(Fig1.) [29,30] and inhibits the generation of pro-inflammatory cytokines such as TNF-α and IL-6.

Targeting Signalling Pathways: Several signalling pathways that are abnormally active in cancer are interacted with by capsaicin(Fig1.). It suppresses the PI3K/Akt/mTOR pathway, an essential signalling cascade that promotes cell division and survival [31,32,33]. Capsaicin has a multifaceted effect on cancer cells by blocking their growth and survival via targeting several mechanisms with the potential of capsaicin as an adjuvant therapy in the treatment of skin cancer

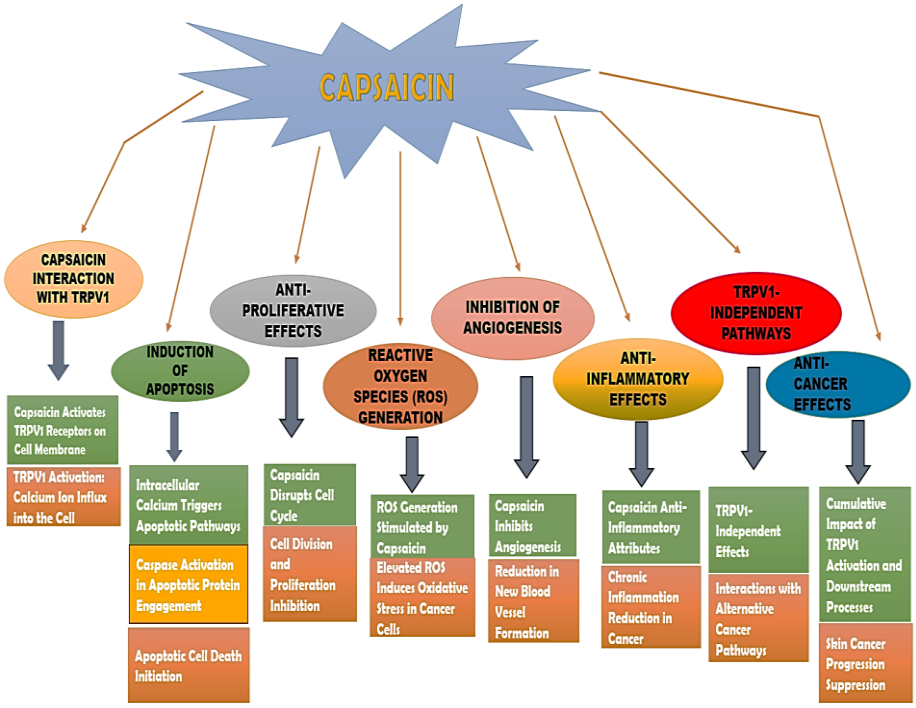


Figure 1: A Comprehensive Overview Elucidating the Multidimensional Mechanisms of Capsaicin in Skin Cancer Progression.

Capsaicin and skin cancer types

Skin cancers are a diverse category of tumours that arise from various cell types and have varied characteristics and Capsaicin has demonstrated potential in treating many forms of skin cancer.

Basal Cell Carcinoma (BCC): The most prevalent kind of skin cancer, basal cell carcinoma, usually starts in the basal cells of the epidermis. It is frequently linked to prolonged sun exposure [34]. Capsaicin can halt angiogenesis, induce apoptosis, and decrease cell proliferation, all of which are crucial factors in the evolution of BCC.

Squamous Cell Carcinoma (SCC): The squamous cells of the epidermis are the source of squamous cell carcinoma, which is also strongly associated with sun exposure and UV radiation [35]. In SCC, capsaicin has pro-apoptotic and anti-proliferative properties as it prevents the growth, progression of SCC by inducing cell cycle arrest[36].

Melanoma: Melanoma is a kind of skin cancer that is extremely aggressive and arises from melanocytes, cells that produce colour. Capsaicin has demonstrated promise in preventing the growth and spread of melanoma cells by affecting signalling pathways linked to melanoma [36]. Furthermore, research has examined capsaicin's ability to obstruct melanoma cell adhesion and invasion, hence impeding the metastatic process .

Subtypes of Other Skin Cancers: Capsaicin has demonstrated anti-cancer capabilities against less frequent, rarer subtypes of skin cancer in addition to the main forms of skin cancer. For example, the potential of capsaicin to target Merkel cell carcinoma, an aggressive and uncommon skin cancer frequently caused by the Merkel cell polyomavirus, has been studied. Capsaicin-containing creams have been investigated for their ability to promote the regression of actinic keratosis lesions, which are a precursor to squamous cell carcinoma [38,39].

Preclinical studies on capsaicin in skin cancer

Preclinical studies play a crucial role in assessing the potential therapeutic efficacy of capsaicin in the context of skin cancers.

In vitro Studies: Numerous skin cancer cell lines have been used to thoroughly investigate capsaicin, which has been found to have a variety of impacts on cell behaviour. Capsaicin has been shown to cause apoptosis and limit cell proliferation in basal cell cancer (BCC) cell lines [32,33,34,40]. Capsaicin has been shown to cause cell cycle arrest and reduce cell growth in squamous cell carcinoma (SCC) models [36,38] and also inhibits cell invasion and proliferation in melanoma cells [37,40].In vitro studies provided evidence of an extensive range of cellular effects of capsaicin. Research studies utilizing lineages of cancer cells provide light on capsaicin's impact on important cell cycle regulators using flow cytometry. Molecular methods such as immunofluorescence and Western blotting are used to identify important markers to understand capsaicin's complex cellular actions, giving potential therapeutic uses [40,41].

In vivo Animal Models: In vivo studies has shown the effectiveness of capsaicin in impeding the formation and progression of tumours. A reduction in tumour volume and weight has been linked to capsaicin therapy in mice xenograft models of skin cancer [41,43]. Furthermore, capsaicin has demonstrated promise in postponing the beginning of tumours and lowering tumour burden in transgenic mice models created to develop skin tumours [42,43,44]. Overall, a thorough grasp of capsaicin's toxicity, delivery methods, therapeutic potential, pharmacokinetics and bioavailability studies , is provided by in vivo investigations paving way for capsaicin's possible conversion into human medicine[42].
Preclinical studies have unravelled several mechanistic insights into how capsaicin exerts its anti-cancer effects. These include:

Activation of Apoptotic Pathways: Capsaicin causes skin cancer cells to undergo programmed cell death through reduction of anti-apoptotic Bcl-2, enhancement of pro-apoptotic Bax and Bad genes independent of TRPV1 receptor (Fig1.). Additionally, by inhibiting NF-κB and AP-1 activation, capsaicin reduces proliferation via reactive oxygen species, inhibits NADH oxidase, and controls IL-8 expression in melanoma. Furthermore, capsaicin inhibits migration via PI3-K/Akt and Rac1, activates death receptor pathways and mitochondria, and down-regulates Bcl-2 resulting in apoptosis[24,41,44,51,52,54].

Suppression of Angiogenesis: Research conducted in vivo has demonstrated that capsaicin inhibits angiogenesis. At dosages lower than those influencing normal cell growth and development, capsaicin significantly suppresses endothelial cell proliferation, migration, and tube formation, particularly a focus on vascular endothelial growth factor (VEGF)-induced angiogenesis arresting cells in G1, leading to downregulation of Cyclin D1 expression. Astonishingly this anti-angiogenic effect occurs despite the vanilloid VR1 receptor being involved. Although capsaicin does not prevent

VEGF from inducing KDR/Flk-1 activation, necessary for angiogenesis, such as phosphorylation of AKT and endothelial nitric oxide synthase (eNOS), p38 MAPK activation, and p125FAK tyrosine phosphorylation. Its distinctive approach to finely regulating angiogenic processes has ramifications for the creation of pharmaceuticals for angiogenesis-dependent disorders, especially skin cancer and other cancers [25,26,27,42,45].

Modulation of Inflammatory Responses: Capsaicin suppresses chronic inflammation, which contributes to cancer risk, by TRPV1-independent mechanisms. Like diclofenac, sub-plantar capsaicin injections exhibit powerful anti-inflammatory effects that limit the release of cytokines including TNF-α, IL-6, and IL-1β in response to lipopolysaccharide (LPS). The mechanism involves dependability on LXRα, inhibition of NF-κB-mediated gene expression through the PPARγ pathway. Furthermore, capsaicin regulates COX-2 and iNOS via suppressing toll-like receptor-mediated cytokine production. Capsaicin modulates inflammation through a variety of pathways (NF-κB, AP-1, STAT1, ERK, JNK, IKK), therefore indicating that this compound could potentially be useful in preventing skin cancer and associated cancers [26,27,42,44].

Inhibition of Cell Proliferation and Metastasis: By modulating important molecular pathways, capsaicin demonstrates its anti-metastatic capability in a wide range of cancer models, including as melanoma, papillary thyroid carcinoma, and oesophageal squamous cell carcinoma (ESCC). By hindering MMP9 through multiple signaling pathways, such as AMPK-NF-κB, EGFR-mediated FAK/Akt, PKC/Raf/ERK, p38 MAPK, and AP-1, capsaicin disrupts the matrix proteolysis pathway, which is crucial for metastasis and impedes angiogenesis. This can be accomplished through downregulating VEGF expression via the p53-SMAR1 auto-regulatory loop. The injection of capsaicin has been shown to greatly lower the metastatic load in mice models, such as the TRAMP model of prostate cancer. This impact is further supported by the upregulation of the tumor suppressor p27Kip1 in treated tumors. Through the detection of vital genes in the TGF-β signaling pathway, computational investigations provide more insight into capsaicin's effects on TGF-β-induced metastasis [26,42,44].

Nanoparticle delivery of capsaicin

Employing nanoparticle-based delivery methods for capsaicin has surfaced as a viable approach to surmount intrinsic obstacles related to the medicinal use of this organic substance. Chilli peppers contain capsaicin, which has a variety of pharmacological characteristics, including anticancer actions. However, problems with its solubility, fast metabolism, and possible off-target effects have made it difficult to apply capsaicin in clinical settings. Nanoparticles provide a clever way to overcome these obstacles. They come in several forms such as liposomes, polymeric nanoparticles, and lipid-based carriers. By acting as carriers, these nanoparticles give capsaicin several benefits, including as increased stability, regulated release, and better bioavailability.

Recent studies have demonstrated that the administration of capsaicin using nanoparticles has become a viable approach in the field of anticancer medication delivery. In an Ahmady et al. (2023) work, regulated drug delivery nanoplatforms with possible anticancer efficacy were created by embedding capsaicin-loaded alginate nanoparticles in polycaprolactone-chitosan nanofibers [64]. With this novel method, the anti-cancer effects of capsaicin—a naturally occurring chemical found in chili peppers—will be increased in terms of therapeutic efficacy. A method of controlled release is made possible by the use of alginate nanoparticles, guaranteeing a steady and precise delivery of capsaicin to cancer cells. In addition to facilitating regulated release, capsaicin integration into nanofibers provides a flexible substrate for drug delivery applications. Using the special qualities of polycaprolactone-chitosan nanofibers and alginate nanoparticles, this innovative technology provides the best possible drug delivery results. Furthermore, the study advances our knowledge of the possible synergistic effects of various formulation ingredients, which might augment capsaicin's therapeutic benefits. It is crucial to take into account the results of relevant research in order to emphasize the importance of this strategy. According to Rollyson et al. (2014), bioavailability is crucial for drug delivery systems, and the effectiveness of capsaicin administration can have a big impact on how well the medicine works [65]. Merritt et al.'s (2022) investigation of sustained release capsaicin formulations and their anti-cancer performance further lends credence to the idea that capsaicin's effectiveness in treating cancer may be increased by controlled, extended exposure [66]. Zhang et al. (2020) studied the wider use of capsaicin in human tumors in light of the increasing interest in the spice as a possible cancer treatment agent[67]. As evidenced by Ahmady et al., the addition of capsaicin to nanoparticle-based delivery systems is a noteworthy development in drug delivery technology [64]. This strategy may help address issues related to capsaicin's bioavailability and solubility, which might lead to the development of more precise and

potent cancer therapies. One promising direction for further study and advancement in the realm of cancer treatments is the administration of capsaicin using nanoparticles.

Targeted delivery systems employing inorganic (metal nanoparticles, carbon spheres), polymeric (micelles, dendrimers, polymersomes), and lipid-based (liposomes, microencapsulation, solid-lipid nanoparticles) nanoparticles have been developed in an attempt to maximize capsaicin's therapeutic impact. Specifically, administration of nanoparticles maximizes medication potency by improving capsaicin retention in the circulation. Improved oral bioavailability and precise, cell-specific drug administration are made possible by modified systems such as liposomes and microemulsions, which may increase cancer cell killing while sparing healthy cells. As evidence of the adaptability of nano delivery in furthering cancer therapy, capsaicin's antioxidant potential extends to the synthesis of biocompatible silver nanoparticles for cancer theranostics [67].Furthermore research studies , In an in vivo rat model, capsaicin-loaded albumin nanoparticles shown concentration-dependent antioxidant activity and decreased TNF-α concentrations when injected intraperitoneally at a dose of 50 mg/kg. These results demonstrate the broad range of applications of albumin nanoparticles as capsaicin transporters, including inflammation and cancer [66,67]. Capsaicin-loaded solid-lipid nanoparticles showed strong anticancer effects against HepG2 cells and were stable in the bloodstream for three days, with an IC50 of 21.36 µg/ml. These results emphasize the potential of capsaicin-loaded nanoparticles, suggesting better pharmacokinetics and greater anticancer activity [68,69]. In chemotherapy-induced peripheral neuropathy, a capsaicin 8% patch not only reduces pain but also encourages the regeneration and repair of epidermal nerve fibres, indicating capsaicin's potential as a helpful adjuvant in managing pain and related side effects during cancer treatment [70].

Clinical studies and case reports

Clinical research and case studies offer vital information about the practicality and efficacy of capsaicin in the management of skin cancer. In recognition of mucocutaneous squamous cell carcinoma, various risk factors such as fair skin type, UVR exposure contribute to carcinogenesis. Capsaicin alters immunological responses, permeability, and vasodilation by inducing the release of neuropeptides. NK-1R antagonists have promise for treating oral cancer. In melanoma, capsaicin functions as a TRPV1 agonist, slowing cell proliferation by regulating PI3-K/Akt pathways [39]. Notable for its ability to desensitize pain, capsaicin continues to be investigated substantially for its analgesic perks, especially in the context of post-surgical, osteoarthritis, and diabetic neuropathy. Although capsaicin can potentially harmful, patients' preference is highlighted when it is used to treat long-term neuropathic pain in cancer patients[29,71]. Although topical capsaicin has been shown in multiple clinical studies to be safe and effective in managing pain for a variety of diseases, its direct relationship to skin cancer has not received enough attention in the literature to yet. While positive outcomes in situations including postmastectomy syndrome, cluster headache, psoriasis, and pruritus demonstrate capsaicin's therapeutic potential[71,72].

Promising results have been seen in studies involving basal cell carcinoma (BCC) patients. Topical capsaicin cream was found to significantly reduce the size and quantity of BCC lesions in a clinical experiment and the efficacy of topical capsaicin in treating BCC lesions in another trial, underscoring the drug's promise as a non-invasive therapeutic alternative[38,73,74,75] . Additionally, the therapy of actinic keratosis, a precursor to squamous cell carcinoma (SCC), has been investigated with capsaicin-containing creams. Actinic keratosis lesions have been shown to regress in clinical studies, which may stop the lesions from progressing to aggressive skin cancer [75,76,77]. Capsaicin-based combination treatments have drawn interest due to its possible ability to work in concert to improve the treatment of skin malignancies. In preclinical investigations, combining capsaicin with other natural substances like resveratrol or curcumin has demonstrated improved anti-cancer benefits. Additionally, co-administration of capsaicin with traditional therapies like as radiation therapy or chemotherapy has shown encouraging results in terms of enhancing treatment outcomes [67,78,79,80]. Notable research highlights the efficacy of capsaicin in treating persistent neuropathic pain, such as the phase II clinical trials employing Adlea (ALRGX-4975) for patients with Morton's neuroma [80]. Further research has emphasized the possibility of using a capsaicin 8% patch to promote nerve fibre regeneration in peripheral neuropathy caused by chemotherapy. Despite the intriguing significance of capsaicin as an adjuvant for pain relief in cancer treatment, its antiproliferative effects in cancer patients remain unknown, demanding additional focused and extensive clinical inquiries[70,71,42].

The potential of capsaicin as a useful adjuvant treatment in the management of skin malignancies is highlighted by these clinical trials and case reports taken together. To determine its effectiveness and safety across a range of patient groups,

further extensive clinical trials are necessary [72-80].

Capsaicin patch: a resilient aid towards skin cancer and pain

The intricate relationships between capsaicin's effectiveness in the fight against skin cancer are revealed by a thorough examination of key factors, such as IC50 values, skin absorption kinetics, and the ideal dose needed to achieve the greatest anticancer effects. Empirical studies have shown that capsaicin-loaded nanoliposomes, especially when applied at a concentration of 8%, significantly lower the IC50 values of a variety of cancer cell lines, such as MCF7, MDA-MB-231, A375 (Table1.), K562, and PANC-1. This decrease highlights capsaicin's excellent therapeutic potential for the treatment of skin cancer. The multifaceted relationship between the physical processes of skin absorption becomes a critical component in deciding how well topical capsaicin therapies work. To deliver a therapeutically appropriate concentration of capsaicin exactly to the targeted skin region, where its anticancer effects are most needed, this strategic optimization is crucial. Extensive studies have repeatedly demonstrated the importance of the 8% concentration in nanoliposomes. This dose is critical for both augmenting capsaicin's anticancer activity and influencing how it interacts with cancer cells [43,71,81,82,83].

Capsaicin's complex role in mucocutaneous squamous cell carcinoma and melanoma has grown increasingly courtesy of recent in vitro studies investigating the survivability of an 8% capsaicin skin patch. This thorough review highlights the remarkable efficacy of the 8% capsaicin skin patch, as evidenced by its potential anticancer effects as well as its ability to treat neuropathic diseases like chemotherapy-induced peripheral neuropathy (CIPN) and postherpetic neuralgia (PHN), despite the occasional contradictory findings. To raise capsaicin's therapeutic benefits to a level worthy of the high standards this thorough analysis sets, the crucial tasks ahead include pinpointing particular routes and doing dose optimization [37,71,83,84,33].

Understanding a complicated dichotomy concerning capsaicin and cancer

A substantial investigation has been conducted on the potential cancer-causing properties of capsaicin, the chemical that lends chili peppers their spicy flavour. The research implemented by Szallasi (2022), Bode and Dong (2011), Liu et al. (2015), and Adetunji et al. (2022) demonstrates the divergent viewpoints present in the scientific debate around capsaicin. This contradiction begs the crucial question: Is capsaicin carcinogenic as claimed, or is it safe until proven otherwise and may even have anti-carcinogenic effects? The purpose of this narrative is to examine capsaicin's dual nature and decipher the intricate details that determine its function in cancer biology. The investigation conducted by Liu et al. (2015) renders a strong case for capsaicin's ability to promote cancer and encountered that skin cancer in mice generated through DMBA and TPA (Table1.) is facilitated by capsaicin. Skin cancers are triggered by DMBA and promoted by TPA in a two-step process. Capsaicin affects the Erk and p38 pathways, which modulates skin inflammation [48]. Bode and Dong (2011) denote capsaicin as having "two faces," implying that due to the fact it stimulates cancer cells to undergo apoptosis, it may have therapeutic promise against cancer. The topical use of capsaicin for pain treatment is surrounded by conflicting data, which presents the idea of desensitization. The work reveals a cocarcinogenic impact on TPA-promoted skin carcinogenesis, involving TRPV1 and EGFR pathways emphasizing on factors like dosage and manner of administration to completely comprehend the detrimental impact of capsaicin on cancer risk [29]. Adetunji et al. (2022) present a comprehensive overview of the worldwide capsaicin research output, providing insights into the field's changing body of knowledge [42]. There is still dispute in the scientific community over the respective effects of capsaicin and cancer, despite conflicting data and viewpoints. The crux of this continuing debate is captured by Szallasi's (2022) question over whether capsaicin is "guilty as charged or innocent until proven guilty". Contradictory research has been found about the complicated relationship between capsaicin and cancer. Furthermore, capsaicin-sensitive sensory neurons inside the tumor microenvironment have a complex function, impacting the development and spread of cancer in a way unique to each cancers [86].

In conclusion, capsaicin's complex dual nature, which presents it as both a possible carcinogen and an anti-cancer agent, calls for more investigation to clarify the circumstances in which it has these opposing effects.

CAPSAICIN CO-CARCINOGENICITY		
Principal Route	**Model of Animal Cell Lines**	**References**
Route incorporating engagement via the epidermal growth factor receptor (EGFR), Upregulation concerning COX-2 catalysed via the epidermal growth factor receptor (EGFR), Akt/mTOR pathway overseen as a result of epidermal growth factor receptor (EGFR), Signalling cascade via Erk and p38	DMBA/TPA-triggered murine model	Bode et al. [45], Hwang et al. [46], Li et al. [47], Liu et al. [48],
CAPSAICIN ANTI-CARCINOGENICITY		
Principal Route	**Model of Animal cell lines**	**References**
Instigation of apoptotic response and proliferation	melanoma cell lines (A375SM, C8161),melanocytes	Marques et al. [49]
Suppresses tumor expansion	Murine melanoma B16-F10 cell	Schwartz et al. [21]
Restraining cytochrome P-450 IIE1 activity	ICR murine strain	Surh et al. [51]
Promotion of apoptosis through mitochondrial pathway ↓Bcl-2 ↑Bax, ↑Bad	Human FaDu pharyngeal squamous carcinoma cells	Le et al. [52]
Downregulation of caspase-activated DNase inhibitor (ICAD)	A375-S2 human malignant melanocytes cell line	Gong et al. [53]
ROS-Induced Apoptosis, TRPV1-Independent Pathway	Oral Squamous Carcinoma Cell line	Gonzales et al.[54]
NF-kB, AP-1 Signalling Axis	Murine ICR model , HL-60 Leukemia Cell Line	Han et al. [55]

Table 1: Overview of studies indicating potential co-carcinogenicity and anti-carcinogenicity of capsaicin demonstrating the primary pathway and experimental models.

Safety and tolerability of capsaicin

Important factors in determining capsaicin's potential as a therapy for skin malignancies are its safety and tolerability. This section investigates the safety profile of capsaicin, contrasting systemic and topical administration, examining side effects and how to handle them, and investigating dose-dependent reactions. There are two ways to deliver capsaicin: topically and systemically. The most popular approach is topical application, and clinical research says topical formulations of capsaicin are typically well-tolerated; the most often reported adverse effects are mild to moderate, temporary burning or stinging sensations [87,88]. Different safety considerations apply when capsaicin is administered systemically, usually via oral intake and also the transient receptor potential vanilloid type 1 (TRPV1) receptors gets activated. Systemic capsaicin can cause nausea, vomiting, and gastrointestinal discomfort, variations in heart rate and blood pressure, when taken at larger dosages [29,39,89]. Lower starting dosages, careful titration, and combination with calming drugs such as menthol or lidocaine are some methods to improve tolerability for topical applications [90]. Clinical investigations are helping to clarify the dose-dependent reactions of capsaicin in humans, which is assisting in the development of dosage plans for secure and efficient care. The key to optimising capsaicin's therapeutic potential is to constantly monitor for unwanted effects and customise the manner and amount of administration based on the unique characteristics of each patient [91,92,93].

Challenges and future perspectives

Capsaicin has encouraging anti-cancer qualities, but there are a number of obstacles towards it efficacious therapeutic therapies for skin malignancies. To fully utilise capsaicin's medicinal potential, these issues must be resolved. One of the major obstacles to capsaicin-based therapy development is creating efficient formulations and delivery methods. Because of its possible irritating qualities and lipophilic nature, capsaicin requires precise formulation to maximise absorption and reduce side effects. Research is being done to improve capsaicin's stability and bioavailability by encapsulation techniques, nano formulations, and targeted delivery methods [39,44,87,94]. Furthermore, the development of novel delivery systems such as transdermal patches or controlled-release formulations provide a prolonged and regulated release of the compound [43,95]. Personalised treatment options are necessary due to the variability of skin cancers. Finding predictive biomarkers for capsaicin-based therapy response is essential. Biomarkers associated with inflammatory markers, p53 status, and TRPV1 expression may be useful for patient stratification [87,96] , along with genetic profiling and molecular characterisation of tumours [37]. Designing robust clinical trials and usage of personalized medicine techniques for capsaicin-based therapies are essential for gathering rigorous evidence of efficacy and safety. Standardised outcome measurements, ideal dose schedules, and suitable patient selection are all taken into account. To prove capsaicin's therapeutic effectiveness in various forms of skin cancer, well-designed randomised controlled trials (RCTs) with sizable patient cohorts are required. Furthermore, include outcomes like overall survival, progression-free survival, and quality of life evaluations can offer thorough understanding of capsaicin's therapeutic effects [91,87,95,97,98].

The development and approval of medicines based on capsaicin are heavily influenced by regulatory concerns. Obtaining market permission requires meeting regulatory requirements for quality, safety, and efficacy. In order to successfully navigate the complicated terrain of medication development and approval procedures, cooperation between researchers, doctors, and regulatory authorities is essential. Multidisciplinary partnerships including researchers, physicians, pharmacologists, and regulatory specialists will be crucial in addressing these obstacles as the field develops and advancing capsaicin-based treatments into clinical use [39,94,95,96,97,98].

Patents

The patent application, titled "Capsicum Extract for Treatment of Skin Cancer," Publication Number: US 20100166895A1Publication Date: July 1, 2010 is attributed to inventor Francisco Silviera Louro from Weston, Florida, USA, describes a way to utilise a capsicum extract to treat skin cancer This extract is made by combining fresh, raw capsicum fruit—especially those from habanero chilli peppers—with a carrier such as vegetable oil, maize oil, or alcohol. On skin regions that require medical attention, the extract is applied topically. Instead of only extracting capsaicin as is customary, the inventor emphasises the usage of the complete fruit of the capsicum. The inventor provides positive case studies to support the extract's ability to treat malignant lesions offering a viable alternate or supplementary therapy option for skin cancer [99].

The patent, entitled "Method for Treating Pre-Malignant Basal and Squamous Cell Lesions of the Epithelium," Publication Number: US006235788B1 Publication Date: May 22, 2001 awarded to James M. Terry and Richard R. Rathmann presents a new strategy for treating pre-malignant skin lesions using capsaicin. The inventors, noticed that due to topical administration of capsaicin lesions became lighter and smaller at a concentration range of 0.010% to 0.200% (w/w) and an average of 0.035% (w/w). Aloe vera and capsaicin can also be combined [100].

The patent Title: Pain Reliever and Method of Use, Patent Number:US6812254B1, Grant Date: November 2, 2004, awarded to Medical Merchandising Inc., introduces a novel pain reliever formulation and its application method as numerous pain and discomfort conditions, including arthritis, neuropathy, post-surgical scarring, itching, can be treated with this novel formulation. Important ingredients in the formulation include capsaicin, histidines, encapsulating agents, amino acid esters, and a light-diffusing substance [101].

The patent ,Title: Compositions and Methods for Cancer Prevention and Treatment using Capsicum Extracts and Tea Catechins ,Patent Number:US20050031716A1,Publication Date: February 10, 2005 filed by Morre D. James, introduces combinations of the anti-cancer capabilities of green tea and the bioactive components found in capsicum extracts—tea catechins—to fight cancer. This combination's synergistic impact offers a viable path towards the development of

successful cancer preventive and treatment plans, marking a significant achievement in the field of oncology [102]. These patents underscore capsaicin's dual properties as both an anti-cancer agent and a pain reliever, showcasing its versatile therapeutic potential.

Conclusion

The review outlines an abundance of data bolstering capsaicin's varied anti-cancer properties. Capsaicin has been shown in vitro to suppress growth, trigger cell death, and alter important signalling pathways in a variety of skin cancer cell types. Preclinical investigations on animals support these results by demonstrating that capsaicin can halt the formation and spread of tumours. Clinical research and case studies offer important insights on capsaicin's practical applications. Oral administration of capsaicin has exhibited potential in treating melanoma, while topical use of capsaicin has demonstrated promise in lowering the size and number of lesions of basal cell carcinoma (BCC). Capsaicin-containing combination medicines have also shown to have synergistic benefits in improving treatment results. The side effects of capsaicin, which are mostly mild burning or stinging sensations, are usually readily tolerated, especially when the dosage is gradually increased. The kind and intensity of side effects are largely dependent on the manner of administration (topical vs. systemic). The findings of this evaluation have important ramifications for clinical and future research in the realm of treating skin cancer. Further research aimed at refining capsaicin formulations and delivery systems will be crucial to improving its therapeutic efficacy. Furthermore, the effective use of capsaicin-based therapy in clinical practise will be facilitated by the identification of predictive biomarkers and the improvement of patient selection criteria.
In conclusion, capsaicin is a viable option in the search for novel treatments for skin cancer. Capsaicin has the potential to revolutionise the area of dermatologic oncology due to its diverse modes of action, proven effectiveness in preclinical and clinical research.

Competing interest

No competing interest is declared between the authors, any commercial industry or organization

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Author contribution

BPC has conceived the article and edited the review work KD,SSR,TS,RP and SB has collected the necessary documents and written the entire document.

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