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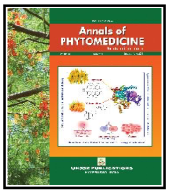

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Unveiling the power of *Capsicum* sp.: Phytochemical insights and therapeutic potential

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Abstract

Capsicum sp. are well-known for their unique flavors and distinct colors. It possesses a variety of phytochemical and pharmaceutical properties. The various phytochemical components of *Capsicum* include capsaicin, capsaicinoids, carotenoids, flavonoids, and volatile chemicals. Capsaicin is a bioactive compound. *Capsicum* exhibits anticancer, antiarthritic, antioxidant, antiobesity, anti-inflammatory, cardiovascular, antidiabetic, antimicrobial, analgesic and gastroprotective properties. *Capsicum* is useful for the treatment and prevention of many chronic illnesses owing to its medicinal properties. It can be employed internally to increase immunity, metabolism, and general well-being and externally as a topical formulation. This review thoroughly discusses the various phytochemicals in chilli and their diverse applications, highlighting their importance as natural cures in contemporary medicine.

1. Introduction

The most common spice in cuisine worldwide is the chilli pepper. *Capsicum* has been grown worldwide since prehistoric times (Kim *et al.*, 2014). The genus *Capsicum* belongs to the Solanaceae family and is commonly known as bell pepper, chilli pepper, hot pepper and sweet pepper. These widely grown vegetable and spice crops are found in tropical and subtropical regions (Olatunji and Afolayan, 2019). In 1498, a crop native to South and Central America was cultivated in India. It is now a necessary component of the Indian cookery due to its unique flavor, color and pungency. In Ayurveda, fruits have been used to treat various ailments since ancient times. Five species have been domesticated; namely, *C. chinense, C. baccatum, C. frutescens, C. pubescens and C. annuum* (Madhavi Reddy *et al.*, 2023). High mineral concentrations, vitamin C, vitamin A and antioxidants such as carotenoids, flavonoids and polyphenols are characteristic compounds of *Capsicum* (Palma *et al.,* 2020). The hybrid produced by crossing *C. chinense* with *C. frutescens* is the hottest chilli pepper in Assam, referred to as bhut jolokia or ghost chilli, ghost jolokia, ghost pepper or simply naga chilli. Assam and other northeastern Indian states, such as Nagaland and Manipur are major cultivators of *C. chinense* (Sarwa *et al.*, 2013). India is the largest producer, consumer and exporter of chillies in the world, contributing approximately 40% of global production. approximately 760, 980 hectares of chilli are grown nationwide, yielding 1,605,010 metric tons annually (Panda *et al.*, 2024). Chilli peppers possess anticancer, antidiabetic, antiarthritic, antioxidant, cardioprotective, analgesic, anti-inflammatory, gastroprotective and antiobesity properties (Sarpras *et al.*, 2019). The most often identified capsaicinoids, a class of strong substances are capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin and homodihydrocapsaicin which are found in green chilli. Owing to of their high concentrations of capsaicin, protein, fixed oil, thiamine and ascorbic acid these compounds have strong pharmacological and physiological effects. A common neuropharmacological component of pharmaceuticals is chilli. Although, fresh chillies are frequently used, it can also be dried or ground into whole, crushed or ground powders. Fresh fruits are also used in pickles, salads, and canned foods. It is vital to add taste to meat, animal products and vegetable soups. Snack foods are also made using the oils and oleoresins present in chillies (Alsebaeai *et al.*, 2020). The most widely used seasoning sauce in the world, pepper is highly prized for its spiciness and provides many meals around the world with a remarkable flavor. It

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was once mostly used as a medicinal plant and flavorings; however, it is now used in crisps, prepared foods and flavorings. It is also grown as a decorative plant and is used to manufacture extracts from various pharmaceutical and cosmetic companies (Tam *et al.,* 2009).

2. Phytochemical profiles of *Capsicum* species

2.1 Capsaicinoids

The main pungent component that gives chilli peppers their pungent qualities are capsaicinoids, which comprise about 69% of the chemicals in the peppers. The amount of capsaicin varies amongst chilli peppers, which results in variations in the fruit's pungency (Srinivasan, 2016). Thresh was the first to isolate crude capsaicin from chilli peppers and coined the term "Capsaicin" in 1876 (Govindarajan *et al.*, 1991). Capsaicinoids are a group of chemicals found in *Capsicum* that share structural similarities and biological properties with those of capsaicin. These chemicals were composed of 69% capsaicin, 22% dihydrocapsaicin, 7% nordihydrocapsaicin and 1% each of homocapsaicin and homodihydrocapsaicin. The pungency of capsaicin is determined by the benzene ring and altered by the acyl chain. Its chemical formula is $C_{18}H_{27}NO_3$ (trans-8-methyl-N-vanillyl-6-nonenamide). Its spiciness is measured in Scoville heat units (SHU), which are based on the amount of capsaicin present. Capsaicin is the main pungent component of *capsicum*. Capasicin (1µg) was estimated to be equivalent to 16 SHU (Hernández Pérez *et al.*, 2020) (Table 1). There are four different levels of pungency in chillies: slightly pungent (700-3000 SHU), pungent (3000-25,0000 SHU), highly pungent (25,0000-70,000 SHU) and extremely pungent (>80,000 SHU). The main capsaicinoids found in hot chillies are capsaicin and dihydrocapsaicin, which together account for 90% of all capsaicinoids. Trace levels of norhydrocapsaicin, homocapsaicin and homodihydrocapsaicin (Hamed *et al.*, 2019). Dawson and Nelson first postulated the molecular structure of the drug in 1919. Using the Micko process, 2.13 g of pure, crystal-form capsaicin was extracted from 1.5 kg of African pepper at 64.5°C (Nelson, 1919). The amide and aromatic catechol rings are retained in all capsaicinoids, giving a chemical structure comparable to capsaicin; however, the quantity of carbon-carbon double bonds and the fatty acid side chain varies. Specifically produced in *Capsicum* species, capsaicinoids possess a distinctive alkaloid molecular structure and capacity to produce pungency. The general chemical structure of capsaicinoids is composed of an alkyl chain and vanillyl group linked by an amide (Fattorusso and Taglialatela-Scafati, 2007). The fruit placenta has the highest concentration of vanillyl amine, where capsaicinoids are mostly produced (González-Zamora *et al.*, 2015). Every capsaicinoid, contains 8-methyl-trans-6-nonenoic acid (capsaicin), 8-methylnonanoic acid (dihydrocapsaicin), 7-methylnonanoic acid (nordihydrocapsaicin), 9-methyldecanoic acid (homodihydro-capsaicin) and 9-methyldec-trans-7-enoic acid (homocapsaicin),which are made from a particular acyl precursor (Liu *et al.*, 2013) (Table 1). After flowering, pungency of the fruit is usually at its highest and capsaicinoid production peaks 30 to 50 days later. After this peak, plant metabolism results in a natural decrease in the capsaicinoid concentration (Fattorusso and Taglialatela-Scafati, 2007). The commercial significance of *Capsicum* sp. is mostly attributed to their savory qualities and biological activity (Nugroho, 2016). The estimated 50% fatal dose of capsaicinoids in humans is approximately 5.0 g per kilogram of body weight but the safe daily ingestion amount is 2.64 mg (Meghvansi *et al.*, 2010). Capsaicin is a molecule that gives a hot, spicy flavor to different types of chilli peppers. Peppers typically contain 0.1 to 1% capsaicin (by weight). The highest amount was found in the Carolina Reaper species (Ed Currie), a cultivar of chilli pepper of the *C. chinense* species, formerly called HP22B. Records showed more than 2,000,000 SHU with an average of 1,569-3000 (Szydeko *et al.*, 2017). The primary biological interaction of capsaicinoids is with the transient receptor potential vanilloid-1 (VR1) a sensory receptor that regulates the response of the brain to pain, osmolarity, temperature fluctuations and acidity (Luo *et al.*, 2011). Capsaicin interacts with TRPV1 receptors in human peripheral nerve fibers, which are responsible for pain perception. The calcium levels of cells rise as a result of this interaction, which causes neuropeptides to be released and signals that interpret intense heat to be transmitted. Extended exposure to radiation may cause inflammatory reactions (Guedes *et al.*, 2018).

Table 1: Capsaicinoids in chilli

S.No.	Capsaicinoids	Abbreviation	Typical proportional quantity
1.	Capsaicin	C	69%
2.	Dihydrocapsaicin	DHC	22%
3.	Nordihydrocapsaicin	NDHC	7%
4.	Homodihydrocapsaicin	HDHC	1%
5.	Homocapsaisin	HC	1%

2.2 Carotenoids

In plants, carotenoids are mostly located in the membranes of the chromoplasts and chloroplasts. Fucoxanthin, lutein, zeaxanthin, violaxanthin, neoxanthin, and α-carotene are among the xanthophylls are separated into these categories (del Rocío Gómez-García and Ochoa-Alejo, 2013). *Capsicum* fruits are categorized as carotenogenic fruits because of their varied carotenoid profiles, which include more than 50 distinct carotenoids (Kim *et al.*, 2016). The color variations observed in *Capsicum* fruits across various species, cultivars and maturity stages are a result of the chromogenic characteristics and profiles (Meckelmann *et al.*, 2015). It is well known that the *Capsicum* sp. is a vegetable high in carotenoid content. Several carotenoids present in the fruit flesh can be divided into pigments yellow, orange and red pigments. The fruit has a range of colors due to these pigments, from light yellow to deep crimson (Mohd Hassan *et al.*, 2019). During the fruit ripening stage, carotenoids form and accumulate rapidly. The fruit is originally green and primarily made up of chloroplasts, which have approximately 68% chlorophyll and 32% carotenoids (Deli *et al.*, 2001). At this stage, common carotenoids such as lutein, violaxanthin, neoxanthin and β-carotene are found in chloroplasts. These carotenoids coexist with chlorophylls and are mostly obscured (Kiokias *et al.*, 2016). The synthesis of chromoplast carotenoids occurs during fruit ripening through the de novo synthesis of new chloroplast carotenoids and transformation of pre-existing carotenoids. Chlorophylls eventually transform into chromoplasts with a variety of carotenoids as the fruit ages. Depending on the particular cultivar, these carotenoids work together to produce a spectrum of fruit hues, eventually turning from green to brown and then yellow, orange, red or dark crimson at full maturity (del Rocío Gómez-García and Ochoa-Alejo, 2013). Variations in fruit content are influenced by growth conditions, ripeness and genotype (Marín *et al.*, 2004). The fruits of chilli peppers are green due to chlorophyll and yellow-orange due to α- and β-carotene, zeaxanthin, lutein and β-cryptoxanthin. Pigments, known as anthocyanins, are purple or violet. Because of oxygenated carotenoids such as those with acylcyclopentanol end groups, chilli pepper fruits are red. Capsanthin, capsorubin, and capsanthin-5,6-epoxide are the most common examples (Sun *et al.*, 2007). During the ripening phase, upto 50% of the carotenoid content of the fruit may consist of capsanthin. The capsanthin structure contains a cyclopentane ring, a conjugated keto group and 11 conjugated double bonds. Violaxanthin accounts for 37% - 68% of the total carotenoids in yellow-orange chilli pepper fruits from *C. baccatum, C. pubescens* and *C. annuum* (Rodríguez Burruezo *et al.*, 2010). Violaxanthin, antheraxanthin and lutein account for 5% - 14%. Because of these properties, capsanthin functions as a potent antioxidant (a good radical scavenger) (Matsufuji *et al.*, 1998).

2.3 Flavonoids

Flavonoids are a class of chemical substances that include over 7000 secondary plant metabolites and are based on a structure with 15 carbon atoms (de Villiers *et al.*, 2016). Flavonoids contribute to growth control, antimicrobial agents, pollinator attraction and UV protection (Rodriguez-Mateos *et al.*, 2014). Flavonoids decrease in concentration throughout ripening, reaching 85% of their levels during vegetative stages (Bae *et al.*, 2014). Flavonoids has anti-oxidant qualities. These enzymes include cyclooxygenase, lipoxygenase, and prostaglandin synthase, which are involved in the development of cancer. Usually found as glycosides, flavonoids have sugars bonded to a three-carbon structure in fruits and plants. Flavonoids are converted into aglycones after ingestion (Batiha *et al.*, 2020). Quercetin and luteolin are the two most frequently detected compounds in fruit tissue in a typical pepper flavonoid assay; their levels can exceed 800 mg kg^{-1} in different *Capsicum annuum*. Fruit from *C. annuum* frequently contains more flavonoids than fruit from *C. chinense* (Howard *et al.*, 2000). Fresh fruit from *C. chinense* was found to have quercetin at levels of 156.96 µg g^{-1} when it was immature and 10.21 µg g^{-1} when it was mature (Butcher *et al.*, 2012). The mature stage of the *C. annuum* cultivar had values of 2.7 µg g^{-1} of fresh fruit, while the immature stage had values of 3.3 µg g^{-1} of fresh fruit. It also prevents viruses from entering and multiplying within the human body (Banu *et al.*, 2024).

2.4 Volatile composition

The aroma of *Capsicum* fruit is attributed to its volatile portion, which also provides bioactivity. More than 200 compounds have been identified in this fraction, including ketones, terpenes, aldehydes, hydrocarbons, alcohols, acids, esters, lactones and phenolics, making diverse and abundant (Patel *et al.*, 2016). The volatile compound composition showed that fruity and sweet odors were more prevalent in the turning and red stages, while most green-related odor volatile chemicals vanished or diminished during maturation. The various species of fresh peppers share common aroma compounds, such as 2-isobutyl-3-methoxypyrazine (green bell pepper), β-ocimen (rancid), octanal (fruity), 2-isobutanedione (caramel), 1-penten-3-one (pungent/spicy), hexanal (grassy, herbal) and 3-carene (red bell pepper, rubbery).

3. Therapeutic potential

Table 2 and Figure 1. provide an overview of the therapeutic properties of five domesticated *Capsicum* sp. and their bioactive compounds.

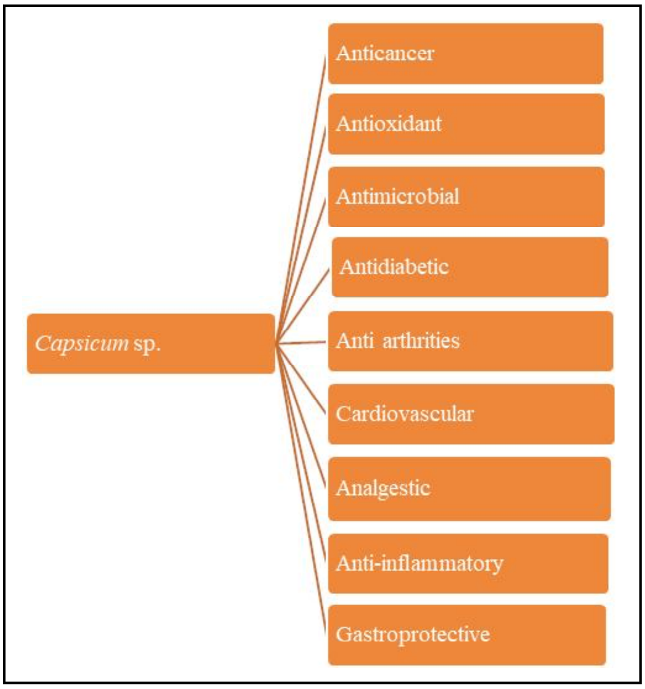

Figure 1: Therapeutic properties of *Capsicum* sp.

3.1 Anticancer properties

One of the causes of cancer worldwide is unchecked growth and dissemination of abnormal cells. Approximately 10 million people die from cancer annually , making it the second leading cause of death globally (Siegel *et al.*, 2018). According to ICMR's 2020 data for India, there will be 1,392,179 cancer patients, with mouth, throat, cervix, tongue and breast cancer being the five most common sites (Khan and Ahmad, 2021). A variety of malignancies, including pancreatic, colon, liver, lung, prostate, breast, bladder and skin cancers are susceptible to the anti-neoplastic effects of capsaicin, the fiery component of hot chili peppers (Zhu *et al.*, 2020). The strong anticancer effects of capsaicin are associated with multiple signaling pathways during different phases of tumor growth, including initiation, promotion, progression and metastasis. It is anticipated that the number of deadliest diseases will increase by more than 70% over the next 20 years (Stewart and Kleihues, 2014). According to scientific studies, capsaicin is considered the best remedy for its anticancerogenic and antioxidant properties, making it the best natural remedy that could soon be widely used in chemoprevention methods (Chu *et al.*, 2002). The prevention of lung, colon, stomach, pancreas, skin and bladder cancers has been demonstrated by capsaicin (Clark and Lee, 2016). One of the most well-described methods on the influence of capsaicinoids on the cancer process was developed using a human colorectal cancer cell line (Yang *et al.*, 2009). Capsaicin kills cells by triggering caspase 3, an essential enzyme of the intrinsic and extrinsic apoptosis pathway that breaks down enzymatic and structural proteins in cells, increases ROS production and alters mitochondrial intermembrane potential and ATP synthesis. In one study, the anticancer properties of capsaicin were confirmed using the human pancreatic cancer cell lines, AsPC-1 and BxPC3. In preclinical *in vivo* investigations, AsPC-1 pancreatic tumor xenografts were orally administered with capsaicin, dissolved in ethanol and then diluted in PBS. This showed that the *in vitro* capsaicin treatment was effective. At 2.5 mg/kg (5 days a week) or 5 mg/kg (3 days a week), capsaicin significantly inhibited the growth of the tumor xenografts. The processes used to induce apoptosis in the animal models were similar to those observed *in vitro*. The research results unequivocally demonstrate that capsaicin is a strong inhibitor of pancreatic cancer growth both *in vitro* and *in vivo* , with no negative effects on healthy cells (Zhang *et al.*, 2008). The potential of this alkaloid to cure bladder and stomach cancers has become promising (Montani *et al.*, 2015). Capsaicin is an effective choice for precisely locating and eliminating abnormal cells, which is essential for the treatment of cancer because it can activate various pathways. This results in cell death. As it inhibits cell proliferation, its potential as a cancer therapeutic agent is further increased (Esakkiammal *et al.*, 2024).

3.2 Antimicrobial properties

Microorganisms are responsible for several food borne diseases and food spoilage each year. Pregnant women may experience spontaneous abortions or stomach discomfort and in extreme situations. These disorders may potentially result in death. Strong antibacterial properties against both good and dangerous microbial strains have been established by the presence of polyphenolic chemicals in *Capsicum* (Akhtar *et al.*, 2021). According to recent research, several chilli pepper varieties and their active components strong antibacterial properties, similar to those of some modern drugs (Raybaudi-Massilia *et al.*, 2017). *Salmonella typhi, Escherichia coli, Bacillus cereus, Staphylococcus aureus, Candida tropicalis, Candida albicans, Candida parapsilosis* and *Candida albicans* are less susceptible to the antibacterial and antifungal properties of capsaicin formulations based on carbopol (Goci *et al.*, 2021). *Capsicum* polyphenolic components have demonstrated exceptional antibacterial activities against both pathogenic and benign microbial strains. Standard strains of both Gram-positive and Gram-negative bacteria were used as test microorganisms to assess the antibiotic sensitivity (Mokhtar *et al.*, 2017). Extracts of capsaicin and its derivative, dihydrocapsaicin from *C. annum, C. baccatum, C. chinense, C. frutescens* and *C. pubescens* have bacteriostatic effects on a range of bacterial species, including both Gram-positive and Gram-negative bacteria (Cichewicz and Thorpe, 1996). Additionally, capsaicin and its derivatives have been shown to inhibit the growth of *Pseudomonas aeruginosa, Salmonella typhimurium, Bacillus cereus, B. subtilis, Streptococcus pyogenes* and *Clostridium tetani* (Koffi-Nevry *et al.*, 2012). The extract of the *C.annuum* bell pepper was injected into ground beef flesh combined with varying quantities of the extract and its inhibitory action against *Salmonella typhimurium* and *Pseudomonas aeruginosa* was tested for seven days at 7°C (Shayan *et al.,* 2013). *C. frutescens* exhibits antifungal and antibacterial properties. It was discovered that CAY-1, a new saponin derived from *C. frutescens*, is effective against 16 different fungal strains and works by rupturing the membrane integrity (Soumya *et al.,* 2012). *C. frutescens's* minimum inhibitory concentration (MIC) was calculated against six strains of Gram-negative (*Klebsiella pneumonia, Escherichia coli, Pseudomonas aeruginosa*) bacteria and gram-positive *(Bacillus subtilis, Staphylococcus aureus, Enterococcus faecalis*) and one strain of yeast. However, the concentrations required for each microorganism were greater than 1000 µg/ml. The fruit extract's MIC (maximum inhibitory concentration) values dropped in comparison to the leaf extracts. The leaf extract showed strong activity against *A. flavus* at the MIC (88.06%), whereas the fruit extract demonstrated activity against *A. niger* in the well diffusion method (88.33%) (Dastagir *et al.,* 2012).

3.3 Antidiabetic properties

According to projections, there will be 537 million more diabetics globally by 2021 than in 2021, 643 million by 2030, and 783 million by 2045. Three out of four adults with diabetes live in low-and middle-income countries. The overall prevalence of diabetes in all 15 Indian states was 7·3%. The percentage of individuals with diabetes in Bihar and Punjab varies from 4.3% to 10.0% (Choudhury and Bhatia, 2024). An increase in insulin resistance in peripheral tissues and lack of insulin generation by pancreatic beta cells are the two main causes of diabetes mellitus. A chronic endocrine disease characterized by problems in the metabolism of proteins, lipids and carbohydrates. Several mechanisms have been demonstrated to explain the antidiabetic effects of *Capsicum annuum*, such as the inhibition of α-glucosidase, and α-amylase, antioxidant activities of the plant's insulin mimetic, weight control, and hypolipidemic effects, and the activation of TRPV1, which improves insulin resistance, lowers inflammation and controls glucose homeostasis. *C. annuum* improves glucose tolerance, increases glucagon-like peptide-1 (GLP1) secretion, decreases fasting glucose/insulin and adipocytokine gene expression and inhibits β cell death in peripheral organs. In traditional African medicine, diabetes mellitus is commonly treated with cayenne peppers or *Capsicum frutescens*. When streptozotocin-induced type 2 diabetic rats were fed a high-fat (HF) diet after four weeks of treatment *C. frutescens* increased their blood insulin levels. Rather than being hypoglycemic, 2% of the dietary *C. frutescens* is insulinotropic (Islam and Choi, 2008).

3.4 Antioxidant properties

Antioxidants prevent oxidation, a chemical process that results in the production of free radicals and damages cells (Vasanthkumar *et al.*, 2024). Phenolic compounds are vital antioxidants that prevent the spread of oxidative stress because it act as radical scavengers and inhibit lipid autoxidation (Melgar-Lalanne *et al.*, 2017). The DPPH free radical assay was used to evaluate the antioxidant potential and free radical scavenging capacities of a few genotypes of chillies from northeastern India. The antiradical power (ARP), efficiency concentration (EC_{50}), and inhibitory concentration (IC_{50}) were measured to accomplish this (Dubey *et al.*, 2015). Three Himalayan red chili varieties in northern India- Kashmiri local, Shalimar long and Kupwari local were tested for antioxidant activity using EC50 values for ferric reducing power, hydroxyl radical scavenging activity and DPPH radical scavenging activity (Ayob *et al.*, 2021). *C. chinense, C. frutescens* and *C. annuum* possess diverse secondary metabolites with antioxidant properties (Hervert-Hernandez *et al.*, 2010). The potency of the antioxidants capsiate, dihydrocapsiate and their related equivalents is extremely strong. Adult men and women who consume *C. annuum* for four weeks have shown an increase in their serum lipoprotein resistance to oxidation, with capsaicinoid antioxidant qualities providing an added benefit in the treatment of cardiovascular disorders (Popovich *et al.*, 2014). Researchers have long been interested in antioxidants because of their potential to improve health.

Food processors have a great opportunity to extract and measure these compounds from various foods because of their numerous documented uses in various food items and nutraceutical products. Vitamins A, C, flavonoids and carotenoids are among the several phytochemicals that are abundant in *Capsicum* fruits (El-Ghorab *et al.*, 2013). Phenolic compounds are vital antioxidants that prevent the spread of oxidative stress because its act as radical scavengers and inhibit lipid autoxidation (Melgar-Lalanne *et al.*, 2017).

3.5 Cardiovascular properties

Cardiovascular disease is one of the main causes of disability and early mortality worldwide. The requirement for efficient cardioprotective measures is highlighted by narrowing of the arterial lumen, which lowers cardiac blood flow. In 2020, the American Heart Association Scientific Sessions found that regular consumption of chili peppers reduce the risk of cardiovascular disease-related death. Numerous sensory neurons in the cardiovascular system are sensitive to capsaicin, implying that capsaicin may aid in regulating cardiovascular function (Vaishnava and Wang, 2003). An anticoagulant found in *C. annuum* helps stop blood clotting, which lowers the risk of stroke. Because it modulates coronary flow through TRPV1 receptor-dependent reduction, capsaicin can prevent heart disease (Guarini *et al.*, 2012). The antioxidant properties of capsaicin and its ability to prevent platelet aggregation are additional benefits. Because of its ability to modulate energy metabolism, the effect of capsaicin on these systems may also contribute to its cardioprotective profile (Juturu, 2016). Dihydrocapsaicin is a capsaicinoid that reduces plasma cholesterol levels, including triglycerides (TG), very low-density lipoprotein cholesterol (VLDL-C) and low-density lipoprotein cholesterol (LDL-C). It also lower the levels of inflammatory cytokines such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), IL-6 and interleukin 1 beta (IL-1β). The high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (apoA1) levels were significantly increased. Additional evidence for these results comes from plasma sterol analysis, which showed that capsaicinoids reduce total plasma cholesterol levels and cholesterol absorption. Dihydrocapsaicin strengthens the reverse cholesterol transport (CRT) route by increasing HDL levels. As a result, foam cells produced by THP-1 macrophages enhance cholesterol efflux and reduce the development of atherosclerotic plaque (Hu *et al.*, 2013). The ability of *C. frutescens* to lyse clots was observed using an *in vitro* thrombolytic model. *C. frutescens*, an *in vitro* thrombolytic model, and honey *C. frutescens* combinations showed 57.40% and 44.54% clot lysis effects, respectively (Takano *et al.*, 2007). The researchers observed that pepper oleoresin decreased blood triglyceride and cholesterol levels by 66% and 70%, respectively, in male gerbils. After rabbits were fed a diet high in cholesterol (1%) and chili pepper (1%) for 12 weeks, it was thought that this effect was caused by a lower intestinal absorption of exogenous cholesterol as a result of the increased biliary excretion of endogenous cholesterol (Gupta *et al.*, 2002). Low-density lipoproteins (LDL), very low-density lipoprotein (VLDL) and cholesterol hematic concentrations were all lower and there was a decreased risk of atheroma formation. Lecithin, a naturally occurring lipid emulsifier found in chili seeds, keeps cholesterol in suspension in the blood and keeps it from accumulating in the arteries. According to several studies, capsaicinoids prevent platelet aggregation.

3.6 Analgesic properties

Capsaicin can reduce pain and discomfort caused by diseases such as diabetic neuropathy, rheumatoid arthritis and neuralgia (Maharjan *et al.*, 2024). Capsaicin eventually reduced pain by lowering the pain signaling route, desensitizing nociceptor fibers, and increasing intracellular Ca^{2+} levels (Braun and Walker, 1996). Subcutaneous administration of capsaicin may efficiently activate the transient receptor potential vanilloid 1(TRPV1) receptor, thereby relieving various pain types (Dupoiron *et al.*, 2022). The reduction in pain expression after plantar incision with 1% capsaicin pretreatment suggests that capsaicin may have a preventative analgesic effect (Guo *et al.*, 2023). Capsaicin is used to treat peripheral neuropathy, particularly in patients with diabeteics, joint and muscle pain, rheumatoid arthritis, osteoarthritis, sciatica and brachialgia. Usually administered as an ointment, it is increasingly advised to use it as a sticking plaster at concentrations of 0.025% or 0.075% because of its poor skin absorption (Frias and Merighi, 2016). A high dose of capsaicin can help patients with brachioradial pruritus and paraesthetic pain quickly and almost without adverse effects.

3.7 Anti-inflammatory properties

Anti-inflammatory illnesses are commonly treated with non-steroidal anti-inflammatory medicines (NSAIDs); however, these medications often have 255 adverse side effects. Consequently, scientists are focusing on plant-based treatments for inflammatory illnesses. This strategy seeks to lower the dangers associated with NSAIDs, in addition to providing efficient pain management (Gobika *et al.*, 2024). The anti-inflammatory properties of capsaicin are linked to the generation of pro-inflammatory mediators and subsequent activation of the TRPV1 channel (Joe and Lokesh, 1997). Research on anti-inflammatory drugs has shown that capsaicin promotes the release of endogenous somatostatin, which helps safeguard the retina from damage caused by ischemia and reperfusion (Wang *et al.*, 2017). Capsaicin may prevent the development of inflammation in the stomach mucosa and joints when the etiology results in higher use of aspirin (acetylsalicylic acid) or ethanol (Fürst and Zündorf, 2014). The production of cytokines that regulate cell responses, including TNF-α, IL-1, IL-6, IL-8, and sticky molecules is greatly disrupted by capsaicin, an agonist of LXRα. This ultimately results in leukocyte migration to areas of persistent inflammation (Tang *et al.*, 2015). Impact on patients with HIV-associated distal sensory polyneuropathy with a single application of a high-concentration capsaicin dermal patch (NGX-4010). Patient pain was reduced for at least 12 weeks after patch application, which proved to be safe. Accordingly, the authors propose that these findings may be applied as a promising novel treatment for HIV neuropathy that causes discomfort (Simpson *et al.*, 2008).

3.8 Gastroprotective properties

The effects of capsaicin on the digestive system include its ability to protect the gastric mucosa when regularly consumed in small doses, at approximately rat body weight (0.1 µg/kg). Exposure of the mucosa to chemicals such as aspirin, 96% concentrated ethanol or a 0.6 molar hydrochloric acid solution results in this protective action (Mózsik, 2014). Thus, capsaicin may help prevent mucosal damage caused by indomethacin. Gastroprotective effects are attributed to the interaction of TRPV1 receptors located in sensory nerve terminals near the gastric mucosa (Matsuda *et al.*, 1999). Capsaicin has been proven as a good medicinal agent that may prevent damage to the gastrointestinal mucosa in cases of long-time treatment with acetylsalicylic acid, especially when patients suffer from coronary artery disease (Sandor *et al.*, 2014). The gastroprotective properties of capsaicin indicate that doses above 10 µg/ml can inhibit the growth of *Helicobacter pylori*, a primary contributor to peptic ulcer disease. However, high concentrations of capsaicin can be detrimental and may cause pathological changes in the liver and gastric mucosa, further studies are needed to determine the best dose based on its pharmacological properties (Toyoda *et al.*, 2016).

3.9 Antiobesity properties

An important medical concern, insulin resistance plays a major role in obesity and non-insulin-dependent diabetic mellitus (NIDDM). As diabetes and obesity reach epidemic levels in the twenty-first century, capsaicin may emerge as an ideal treatment because of its diverse effects on lipid metabolism. In brown adipose tissue, strong TRPV1 receptor agonists such as capsaicin, dihydrocapsaicin and capsiate are known to increase the levels of proteins involved in thermogenesis and can aid in preventing the transformation of preadipocytes into white adipocytes (Yoneshiro and Saito, 2013). These natural substances are promising dietary supplements that activate fatty acid oxidation in the liver and adipose tissues, thereby preventing and combating obesity (Kang *et al.*, 2010). Gene expression codes for reductase were measured to assess the degree of change in activity. CPT-1 (carnitine palmitoyltransferase I, an enzyme of β-oxidation of long chain fatty acids), FAT/CD36 (integral membrane protein involved in the uptake of long-chain fatty acids), GLUT4 (glucose transporter type 4, responsible for transporting glucose to a cell in an insulin-dependent mechanism) and HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A, an enzyme involved in mevalonic acid transformations and is involved in the production of cholesterol and other isoprenoids). All of these genes showed a marked increase in expression. Furthermore, there was a reduction in fat deposition in the adipocyte tissues. Other pathways of capsaicin-induced metabolic modulation have been confirmed in numerous studies. CAP helps individuals lose weight because it causes the adrenal medulla to secrete more noradrenaline and adrenaline (Hong *et al.*, 2015). In additionally, capsaicin controls hunger. It promotes feelings of fullness after meals and decreases hunger for fatty, salty and sweet foods (Yuan *et al.*, 2016). Transient receptor potential vanilloid 1(TRPV1) receptor activation occurs when capsiate is consumed orally. This stimulation subsequently stimulates thermogenesis by increasing fat tissue lipolysis through the sympathetic nervous system (Yashiro *et al.*, 2015).

3.10 Antiarthritic properties

Many forms of arthritis can be made less painful using capsaicin cream. In particular, it functions by reducing substance P, a naturally occurring substance in the human body that aids the transmission of pain signals to the brain (Dhamodharan *et al.*, 2022). The growth of arthritis was effectively controlled by ethanolic extracts of *C. annum*. The leaf extract of *C. annum* significantly decreased adjuvant-induced arthritis (AIA) arthritis scores (Tag *et al.*, 2014).

Table 2: The role of capsicum and its biocomponents in health

Capsicum species	Common name	Therapeutic properties	Active compounds	Reference
Capsicum annum	Bell pepper,	Antimicrobial	Capsaicin and	Kosuge and Faruta, 1970
	Sweet pepper	antidiabetic	dihydrocapsaicin	Careaga *et al.*, 2003
Capsicum baccatum	Aji, Aji amarillo, Locoto	Anti-inflammatory	Antioxidant	Allemand *et al.*, 2016
Capsicum chinense	Bhut jolokia/ghost chili	Analgesic, anti-inflammatory, anticancer, anti-arthritic, gastric ulcer protective	Capsaicinoids Carotenoids	Rastogi *et al.*, 2024
Capsicum frutescens	Bird eye chilli	Antidiabetes, antibacterial	Capsaicinoids	Dhamodharen *et al.*, 2022,
			Carotenoids	Bello *et al.*, 2015
Capsicum pubescens	Rocoto/tree pepper	Antibacterial	Capsaicin	Meckelmann *et al.*, 2015
			Dihyrocapsaicin	
			Nordihydrocapsaicin	

4. Usage

4.1 External use

There are several externally applied types of capsaicin and *capsicum* creams that range in concentration from 0.025% to 0.075% and can be applied three to five times daily. *Capsicum* plasters, which contain 345.8 mg of powdered *Capsicum* and 34.58 mg of tincture per sheet (12.2 × 16.4 cm), have been evaluated for postoperative pain and nausea (Kim *et al.*, 2009). Capsaicin can be topically used as an active ingredient in patches and ointments. These patches, which contained a concentrated extract of *C. annum*, were applied to the skin for 30-60 min. In low-dose formulations (0.025% and 0.075%), its deliver 6-8 µg/cm² of capsaicinoids, whereas in high-dose formulations (8%), 0.64 mg/cm² of pure capsaicin. Particularly for recurrent pain, treatment may be repeated at least 90 days after the initial session (Laklouk *et al.*, 2016). Nonivamide, a synthetic capsaicin, is widely used as a warming ingredient in ointments (0.025-0.05%) to relieve muscle pain, *ad hoc* neuralgia and arthritis. It is typically applied 1-2 times daily for a maximum of two days. There must be a minimum of 14 days between applications at the same position (Yu, 2011).

4.2 Internal use

The daily intake of capsaicin ranges from 25 to 200 mg/person/day in nations with spicy cuisine. It is recommended that 0.5 to 4 mg/kg/day for a person weighing 50 kg. For countries such as the USA and Europe, lower doses of 0.025 mg/kg/day are recommended (Zhang *et al.*, 2008). Lipid-based capsaicin formulations are used to enhance absorption, reduce the hot and spicy taste of the molecule and decrease the risk of negative effects on the mucosa of the gastrointestinal tract.

5. Future prospects

Future advancements in capsaicin delivery systems are likely to enhance its bioavailability through innovative methods such as iontophoresis, hydrogel formulations and liposome encapsulation. Recent developments in nanotechnology have led to the development of sustained-release capsaicin formulations. These promising formulations aim to deliver capsaicin more effectively and persistently to the target organ sites. In the future, combining capsaicin nanoparticles with other medications for combination therapy could enhance the treatment effectiveness. Additionally, addressing the adverse effects of capsaicin using second-generation capsaicin mimetics, which demonstrate greater pharmacological activity, presents another promising strategy. Incorporating *Capsicum* extracts into functional meals may enhance the health benefits of regular diets. The formulation of these foods to improve bioactivity and nutrient absorption should be investigated in future studies. Dietary decisions can be influenced by increasing consumer knowledge of the health advantages of *Capsicum* species. Protecting consumer interests and encouraging corporate innovation depend on the establishment of precise regulatory criteria for the efficacy and safety of these bioactive compounds. We can increase the use of chemicals produced from pepper by addressing these important concerns, which will lead to the creation of sustainable, natural goods in various industries that will eventually benefit both public health and the industry.

6. Conclusion

There is great potential for several enterprises to produce *capsicum* fruits and their constituent parts. The textile and agro-food industries have also demonstrated the benefits of the byproducts this plant. The effects of capsaicin and its natural forms on the human body are complex and involve several molecular and metabolic processes. Capsaicinoids are used in therapeutic contexts of their well-studied anti-inflammatory and analgesic properties, which are mostly mediated by the TRPV1 receptor. According to research on the gastroprotective properties of capsaicin the TRPV1 receptor may be a promising target for the treatment of peptic ulcer disease and chronic gastritis. Several *Capsicum* cultivars and their derivatives have become increasingly popular in recent years. *Capsicum* plants have numerous applications in various of sectors, such as agriculture, food, medicine, pharmaceuticals and cosmetics. People increasing awareness of health issues and their continuous search for healthy, nourishing food have led to the development of chili as a functional foods, cosmetic ingredient, and medical supplement in recent years, especially in the dietary sector.

Conflict of interest

The author declares no conflicts of interest relevant to this article.

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