

Capsaicin–TRPV1 Signaling: Therapeutic Potential, Molecular Mechanisms, and Safety Considerations

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Abstract

Hot peppers (*Capsicum* spp.), particularly *Capsicum annuum*, have been consumed worldwide for centuries as food, medicine, and natural colorants. Their pungency is primarily attributed to capsaicin, a bioactive alkaloid synthesized in the placental tissue of chili fruits. Capsaicin exerts its biological effects mainly through activation of the transient receptor potential vanilloid 1 (TRPV1) receptor, a non-selective cation channel involved in nociception, thermoregulation, and neurogenic inflammation. This review highlights the dual role of capsaicin as both a health-promoting and potentially harmful compound. Numerous experimental and clinical studies demonstrate its beneficial effects, including anti-inflammatory, antioxidant, anti-obesity, anti-diabetic, cardioprotective, neuroprotective, reno-protective, and anticancer properties. Capsaicin has also shown therapeutic potential in conditions such as alopecia areata, colitis, hepatic steatosis, pneumonia, renal injury, and metabolic disorders through modulation of lipid metabolism, oxidative stress, gut microbiota, and cellular apoptosis. Conversely, excessive or prolonged exposure to capsaicin has been associated with adverse outcomes, including gastrointestinal injury, chronic cough hypersensitivity, gut dysbiosis, neurogenic pain, central sensitization, vasoconstriction syndromes, and tissue damage. Additionally, contamination of chili products with aflatoxins poses further health risks. Overall, this review emphasizes the “capsaicin paradox,” underscoring the importance of dosage, exposure duration, and physiological context in determining whether capsaicin functions as a therapeutic agent or a toxic irritant.

1. Introduction

Hot pepper which is also known as chili used in ancient times for a variety of purposes such as traditional medicine, natural colorants, flavoring agent, and food vegetables. There is a wide variety of peppers including sweet and pungent peppers which are consumed worldwide. The most common type of commercial pepper of a wide variety is *C. annuum* (Hernández-Pérez et al., 2020). Chilies are highly valuable due to their bright red color and higher pungency. Capsaicin (C₁₈H₂₇NO₃) (N-vanillyl-8-methyl-6-(E)-none amide) is the important component that causes pungency in chili. A higher level of capsaicin leads to hotter chili. This substance causes heat sensation and stimulates the human body to trigger heat receptors. I.e. Transient Receptor Potential Vanilloid (TRAP1). Capsaicin is manufactured in seed-bearing membranes of fruit (Arim, 2019). Chilies derived in the northern basin and so by natural geographic scatter are indigenous throughout the West Indies, South America, Central America, and most southern States of America. The oldest variety of chili are Tenpin and chiltepin pepper and also known as mother chili. It grows in the regions of Arizona, Mexico, and Texas which is now the state of chili. These areas receive very little rainfall such as the Sonoran desert. It is found thriving in the partial shade provided by Mesquite or Desert Oak. In these conditions, this supposedly annual plant has been known not only to survive but also to give fruits for up to 20 years which is maximum of all other plants. The most interesting aspect of most chilies if they are in suitable conditions they will not only flourish many years but also will become more prolific fruits in the 3rd and 4th years. (Madala and Nutakki, 2020).

Capsaicin is produced as a natural defense against fungi and herbivores. Capsizing causes an increase in gastric secretions and salivary secretions, a decrease in blood pressure, and increased intestinal activity. Capsaicin is present in high quantities in the placental tissue. Capsaicin is a health-promoting substance that helps to protect from various diseases. It is a neuropeptide active agent which affects the release of substance P, transport, storage, and synthesis. It is a principal chemical mediator in pin impulses from the peripheral to the central nervous system. It prevents the accumulation of substance P in joints and skin and makes them insensitive to pain. Pain impulses are not transmitted to the brain with depletion of substance P. Chili peppers are a spice vegetable crop containing many bioactive compounds pharmacologically active compounds with potential health benefits, phytonutrients, phytochemicals, capsaicinoids, and flavonoids. These compounds make them effective against dreadful diseases such as microbial

diseases and cancer, inflammation, diabetes, obesity, and coagulation. They have scavenging ability to oxygen and free radicals and are known as antioxidants (Bal et al., 2022).

1.1 The capsaicin paradox

The human which are exposed to capsaicin are enormous with an estimated 2 billion chili peppers connoisseurs worldwide. The question of whether capsaicin can cause cancer or it is a preventative agent is extremely important (Szallasi, 2022). Capsaicin has both positive and negative effects so it acts like a double-edged sword. Positive effects of capsaicin include maintenance and protection of the body including antivirals, and biofilm, antibacterial, inflammation, pain reduction, gastrointestinal, body weight, and cardiovascular. While the negative effects around its co-carcinogenic effects are produced by two products released by capsaicin i.e. calcitonin-related gene protein and substance P. these are stimulated by the TRAP1 agonist receptor. These products are irritants and initiate the activation of mast cells, and cause neurogenic inflammation. (Sunariani, 2021).

1.2 TRPV1 mechanism of action

Transient receptor potential vanilloid 1 (TRPV1) is calcium permeable ion channel which has a pungent property in the red chilli and several other chemicals are found in capsaicin.. It acts as a detector of painful stimuli and is expressed in a sensory neuron. Pungent chemicals and high temperatures are responsible for producing painful stimuli. It is crucial in nociceptor signaling because its activation is sensitized by several endogenous second messengers and inflammatory mediators. Activation of TRAP1 control different organ functions (Shuba, 2021). These included facilitating the release of neuropeptides from sensory fiber signaling function. TRAP1 is present still complicated mechanism. These are found in many different regions such as in adipocytes, immune cells, epithelial, some smooth muscles, and skeletal muscles (Munjuluri et al., 2021).

TRAP1 is a poly model protein that plays a significant role in the production of pain. Capsaicin has a significant vasoconstrictor effect and has severe negative effects on the body such as myocardial infarction and vasospasm when it is consumed in excess amounts. This is due to the fact that the vascular TRAP1 channel activates capsaicin in the body. The review article explains both the negative and positive health conditions of dietary capsaicin in light of recent research.

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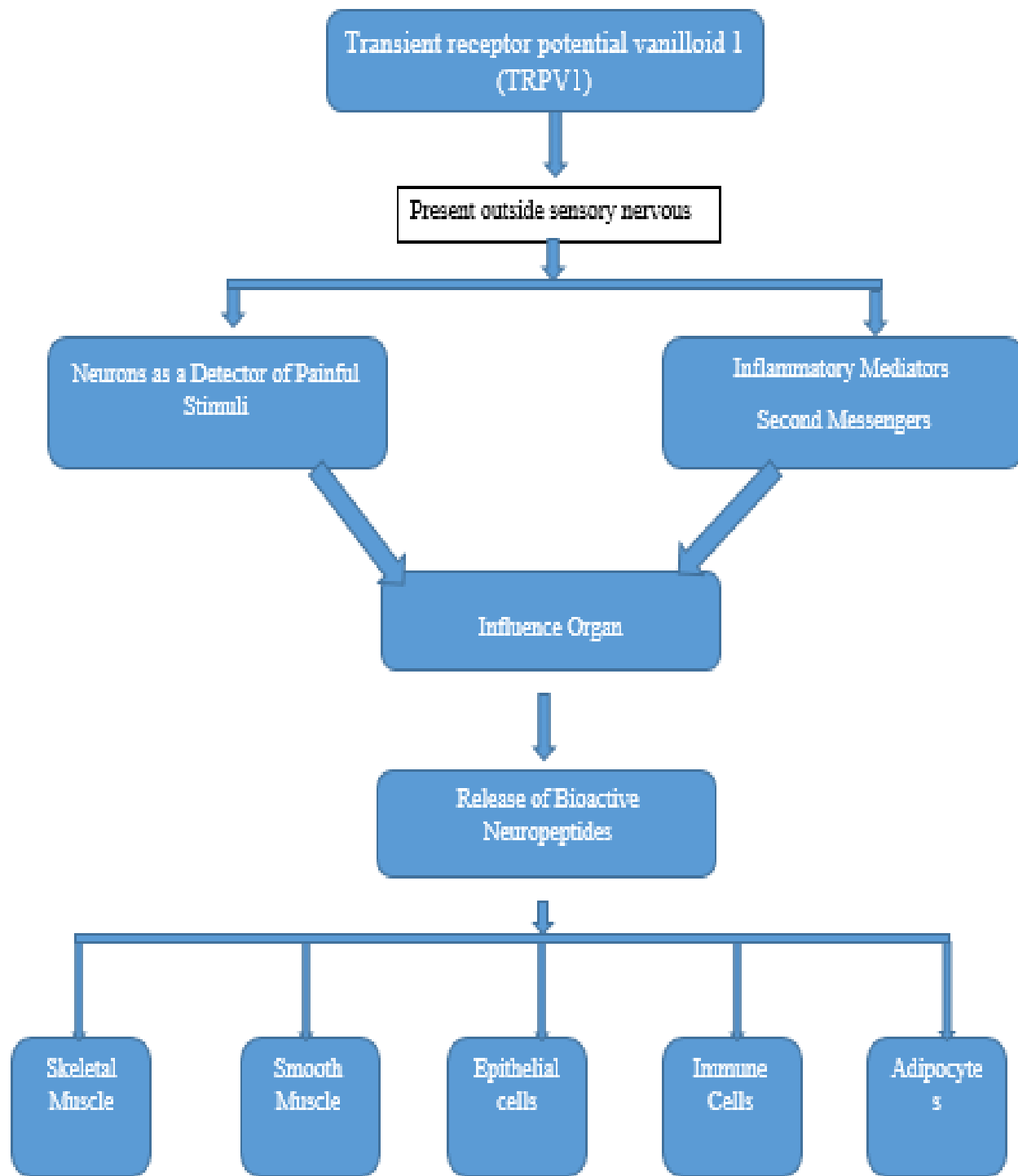


Figure 1: TRPV1 activation and downstream neurogenic and cellular effects

2. Advantages of capsaicin

Capsaicin exerts diverse biological effects through activating and modulating TRPV1. It also offers several potential therapeutic benefits. The major advantages of capsaicin found in the literature were summarized in Table 1.

Table 1: Advantages of Capsaicin

Subjects	Route of Exposure	Methodology	Findings	References
Mice	Iodixanol injection Intraperitoneal capsaicin injection	four groups. CA-AKI group CA-AKI+CAP group CA-AKI+vehicle group. Control group	Capsaicin prevents acute renal injury and dysfunction in CA-AKI.	(Bellen et al., 2020)
Humans	Load cycling exercise	n=20 Double blinded study n=10 (placebo) n=10 (experimental)	(p >0.05) No significant cardiorespiratory responses CAP attenuated the reduction in potentiated twitch	(Gaia et al., 2022)
Humans	Oral administration of high fat diet (10 weeks)	Four groups (n=8 in each group) HFD group (508 kcal/100 g) Normal group (360 kcal/100 g) HFD + EPA group EPA + CAP group	Body weight of HFD and EPA group higher Body weight of EPA+ Cap group significantly lower (p<0.01)	(Yoshihiko et al., 2017)
Mice	Leptin receptor- deficient diabetic male mice	Two groups (n = 8 per group) Group 1 (Chow diet) Group 2 (chow diet with 0.01 % CAP) 8 weeks All groups treated with antibiotics	CAP Administration Protects mice from Glucose Intolerance and Insulin Resistance	(Socheng et al., 2019)
Humans	Topical Ointment	2 groups Topical treated with the mixed preparation (case) twice daily 5%minoxidil (control) once daily for 3 months.	mixed preparation of piperine, capsaicin, and curcumin is effective in treating alopecia areata	(Yaqi et al., 2020)

Rats	Oral administration of the sulfated polysaccharide DSS	Two groups n= 10 Group 1 water with 2.5% DSS Group 2 combination of 2.5% DSS plus capsaicin	Capsaicin induces endothelium-dependent vasorelaxation (2) TRPV4/EDH signals play a critical role in the capsaicin-induced submucosal arterial relaxation (3) capsaicin exerts anti-colitis action by rescuing the impaired endothelium-dependent vasorelaxation via TRPV4/EDH pathway.	(Luyun et al., 2022)
Sprague-Dawley rats	Orally administered high fat diet for 4 weeks	(n = 8) Samples were placed in sterile doffer tubes frozen in liquid nitrogen for 30 sec, after which they were stored at -80°C	CAP decreases weight gain, liver weight and food intake	(Ting et al., 2022)
Humans	Patient with diabetic neuropathy recruited	Three groups based on their treatment regimens; Group LL (Lidocaine + Lidocaine), Group LP (Lidocaine + Placebo), Group LC (Lidocaine + Capsaicin).	Group LL: 6.4 ± 1.5, Group LP: 6.1 ± 1.6, Group LC: 6.7 ± 1.9 with an average daily pain score as 6.2.	(Nadia et al., 2022)
Humans	Neurogenic Dysphagia patients recruited from hospitals	n=30 (Control group) Aerosolized capsaicin 1 drop of liquid cayenne extract (n=30)	ND group: reflexive PCF was significantly higher (p = 0.001) In the control group, reflexive PCF was significantly lower (p < 0.001).	(Ellian et al., 2022)
Humans	Topical ointment	n=29 (old bedridden dementia inpatients at high risk of aspiration), treatment for 6 months	Incidence of pneumonia Before intervention 1.80 ± 0.37 After intervention decreased to 0.40 ± 0.29 (p < 0.01)	(Osamu et al., 2020)
Male Sprague-Dawley rats	Oral administration (High fat diet was premixed with curcumin (1.5 g/kg HFD) and/or capsaicin (0.15 g/kg HFD)	n=40 Control group (n=8) HFD group (n=8) HFD+CUR group (n=8) HFD+CAP group (n=8) HFD+CUR+CAP group (n=8)	Combination of curcumin and capsaicin led to the reduction of TBARS levels in the testis CAT activity was elevated in curcumin and/or capsaicin treatment rats	(Sveda et al., 2019)

Female Wistar rats	300 g L ⁻¹ sucrose solution orally to induce (Hypoestrogenic and Obesity) for 28 weeks.	Two groups HE groups (normal diet) HEO groups (Sucrose diet) Each group into four experimental subgroups HE-Sed (n=6) HEOb-Sed (n=6) Ex: HE-Ex (n=4) HEOb- Ex (n=5) Cap: HE-Cap (n=6) Cap: HEOb-Cap (n=7) Cap+Ex: HE-Cap + Ex (n=4) HEOb-Cap + Ex (n=5)	(Cap + Ex) treatment reduced Body fat, body weight, oxidative stress, Hepatic steatosis. CAP treatment reduced BP	(Juana et al., 2020)
Mice Clinically: Human hepatocyte	Orally induced feed Topical capsaicin ointment	Two groups Normal diet (n=9) HFHSD (n=16) HFHSD subjected to capsaicin cream WRL68 cells	Topical application of capsaicin significantly decreased liver index (HFHSD vs HFHSD + Cap, 6.92 ± 1.47 vs 6.16 ± 1.13, mean ± SEM, n = 8) Capsaicin treatment decreased intracellular lipid accumulation in human hepatocytes.	(Jing et al., 2022)
Mice	Oral gavage, Stock solution of CAP	Two groups Adult male C57BL/6 J strain WT mice and TRPV1 KO mice	Oral gavage of CAP induces acute change in core body and tail surface temperature	(Inagaki et al., 2019)
Human prostate cancer cells	Capsaicin treatment	PC3, DU-145 and LNCaP human prostate cancer cell lines, routinely grown in RPMI 1640 medium supplemented, incubated at 37 °C in 5% CO ₂	capsaicin exerts antiproliferative effects in prostate cancer cells expressing LKB1 by a TRPV1 receptor-dependent mechanism	(Sánchez et al., 2022)
Human lung cancer cells	Capsaicin treatment	cells were maintained in Dulbecco's modified Eagle's medium, containing 5% fetal bovine serum 100 Unit/mL penicillin, and 100 µg/mL streptomycin at 37 °C in an incubator	inhibition of cell growth and HIF activation in lung cancer cells	(Han et al., 2022)
Mice	Orally induced Capsaicin and genistein	Six groups N=6 (each group) All compounds were dissolved in 20% DMSO in saline.	Co-administered genistein Capsaicin reduced Weight, adipocytes and triglycerides	(Reddy et al., 2020)

			Genistein showed no effect	
Mice	Capsaicin and mucin (HFD) given orally	Male C57BL6/J mice (aged 4–6 weeks) pathogen-free environment at 25 ± 2 °C, 12-hour light-dark cycle. After 1 week divided into 4 groups randomly.	Capsaicin and mucin prevented HFD-induced metabolic complications in mice	(Kumar et al., 2022)
3T3-L1 cells	Capsaicin and genistein	Capsaicin, genistein, ethanedithiol (EDT), insulin, dexamethasone, 3-isobutyl-1-methylxanthine (IBMX), oil red O stain chemicals for RNA extraction using Trizol method were procured.	MTT assay showed capsaicin did not affect 3T3-L1 cell viability until 10 μ M concentration and genistein till 100 μ M	(Reddy et al., 2019)

2.1 Capsaicin diminished alopecia areata

Alopecia areata is a non-scarring hair loss that is caused by T cells. This is the most common hair disease which takes place in most of the population. Capsaicin is used for the regrowth of hair. Capsaicin plays a significant role in curing this disease by improving blood circulation in the scalp and the anti-inflammatory effect to reduce this disease. According to (Mao et al., 2022), it is explained that capsaicin helped to reduce this disease. This study was performed on patients who were suffering from alopecia areata. People were separated into 2 different groups randomly and capsaicin was administered topically twice daily. On the other hand minoxidil, 5% was used as a control experiment which was administered once on daily basis. Hair loss was assessed with the help of dermoscopy and SALT. As a result, it was explained that there was a significant regrowth of hair in people who have alopecia areata. Capsaicin was 63.33% more effective against alopecia areata. Thus capsaicin was responsible for the regrowth of hair and prolonged the growth period of the hair. Thus it is essential to control hair loss and be effective against this disease.

2.2 Capsaicin decreased colitis

Vascular endothelium regulates functional activity as well as maintains the structural integrity of blood vessels. Endothelial dysfunction can lead to several other chronic diseases such as diabetes, heart disease, and hypertension. Capsaicin maintains the tone of endothelium-dependent vasodilator and has therapeutic potential against many vascular diseases. It decreases pain and inflammation in the body. Human submucosal arterioles control blood flow perfusion in intestinal mucosa to maintain barrier function. According to (Zhang et al., 2022), capsaicin was used to maintain the vasodilation and relaxation of the endothelium. This study was conducted to determine the role of capsaicin and mesenteric circulation during colitis. It was analyzed whether capsaicin could ameliorate colitis or not. The study was conducted on mice Mulvaney-style wire myograph was used for the functional assessment to assess the endothelium. Calcium and membrane potential were analyzed through the calcium-sensitive fluorescent dye as shown in Figure 2.

Mice were administered with drinking water containing 2.5% DSS and capsaicin. As a result, it was deduced that endothelium-dependent vasodilation was induced by the intake of capsaicin along with exerting anti-colitis action by repairing impaired endothelium-dependent vasorelaxation. It modulates TRPV4/EDH pathways which play a critical role in submucosal arterial relaxation. Thus capsaicin helps to reduce the symptoms of colitis by improving endothelium.



Figure 2: Capsaicin-Mediated Vasodilation

2.3 Capsaicin regulates lipid metabolism

Capsaicin is the most functional ingredient which reduces the fat content in the body. Abnormalities in lipid metabolism are regulated through capsaicin which is linked with several metabolic diseases. It diminished lipid metabolism imbalance and inhibits excess storage of fats. According to (Gao et al., 2022), it is evaluated that capsaicin elevates satiety and decreases appetite by reducing blood lipid levels. Gut microbiota played a significant role in regulating these metabolic pathways. Capsaicin also maintains these different microflorae that regulate functions in the body. Various inflammatory factors are also reduced. This study was conducted to determine the mechanism which was used to regulate lipid metabolism. It helped to analyze the role of capsaicin to regulate lipid metabolism. 8 rats were obtained and placed in sterile doffer tubes frozen in liquid nitrogen for 30 seconds and stored at -80 C. Venipuncture was used to obtain the blood samples of these mice which were analyzed. Plasma triglycerides and cholesterol were calculated along with LDL, HDL, and SCFA. As a result, it was explained that CAP was used to reduce food intake, liver weight, and weight gain. CAP improved serum fasting insulin, fasting plasma glucose, hepatic lipid, and dyslipidemia.

2.4 Capsaicin reduced the incidence of pneumonia

Pneumonia is the major cause of death in most of the population worldwide. The cough reflex protects foreign bodies from entering the respiratory tract and prevents microbial growth. Capsaicin induces cough reflex and thus reduces the incidence of pneumonia. According to (Jinnouchi et al., 2020), it is evaluated "capsaicin improved glottal closure and cough reflexes in elderly patients with dysphagia. It enhanced the cough reflex as a glottis protective measure, resulting in the reduction of pneumonia development in elderly dementia patients at high risk of aspiration. It caused stimulation of pharyngolaryngeal mucosa which helps to reduce pneumonia". In this study, 29 bedridden patients were obtained who was suffering from dementia and pneumonia. An ointment containing 0.025% capsaicin was given to these patients. This substance was administered through cotton swabs in the auditory canal for 6 months. As a result, it was deduced that the incidence of pneumonia was reduced significantly after 6 months from 1.80 to 0.40. No adverse effects of the compound were found in this experiment. Angiotensin-converting enzyme inhibitors were involved in the reduction of this disease. Capsaicin promoted several cough responses which reduced the growth of the foreign substance.

2.5 Capsaicin decreased hepatic oxidative stress

A high-fat diet is a problem that is present among most people. It is a life-threatening condition that decreases the quality of life. As explained by (de Lourdes Medina-Contreras et al., 2020) Intracellular triglycerides in hepatocytes increase oxidative stress in human beings. Natural Antioxidants can prevent the formation of free radicals and decrease oxidative stress in the human body. Capsaicin present in red pepper has antioxidant and anti-inflammatory properties to decrease oxidative stress. Capsaicin caused apoptosis and inflammation in abnormal liver cells. The purpose of this study was to analyze the antioxidant status of capsaicin on a high-fat diet. It helped to analyze the levels of antioxidants in the Rats were divided into 5 groups and a high-fat diet is given to these male rats including capsaicin. This diet was administered for approximately 16 weeks and TBARS and enzymatic, and no enzymatic reactions in the liver were measured. Protein levels were also analyzed by bicinchoninic acid. TBARS levels were increased in the HFD group and ROS level was not found. In this group, no degenerative damages were present which were caused by ROS.

2.6 Capsaicin decreases lipid accumulation in the body

Capsaicin is responsible to decrease the number of lipids in the body by preventing lipid accumulation in the body. According to (Reddy et al., 2019) it was explained that satiety peptides send signals to the hypothalamus which helps in the regulation of food intake and appetite. In this way, it helps to control the diet. Capsaicin acts as an anti-obesity and reduces fat accumulation. This was carried out by increasing thermogenesis by elevating the catecholamine secretion level. Obestatin upregulates glycerolipid metabolism. Genistein is also another isoflavone that works synergistically with capsaicin and decreases body weight gain visceral and hepatic fat storage by fatty acid oxidation. The purpose of this study was to know that administration of capsaicin along with Obestatin and genistein could reduce the levels of triglycerides and help to handle the accumulated fat. When they work synergistically they could decrease obesity. 3T3-L1 cells were obtained. Capsacin, Obestatin and genistein were added in the cell. These cells were cultured and maintained. Oil red O staining and determination of triglycerides level were carried out on the cells. As a result, it was explained that the MTT assay showed that capsaicin alone did not reduce levels of fat until

genistein is added to a higher proportion. So they work according to each other. Levels of lipids were also decreased when the three compounds capsaicin, genistein, and Obestatin were added to the cell.

In another study, the anti-obesity effects of capsaicin were explained. Probiotic bacteria activated TRAP1 which is the most useful component for the activation of capsaicin. According to (Kumar et al., 2022) Capsaicin decreases the secretion of mucus by activating the mucin gene. The purpose of this study was to explain the role of TRAP1 to decrease mucus secretions which alleviates high-fat diet impairment leading to obesity. Male mice were obtained in this study and capsaicin and mucin were given orally. A high-fat diet was given to these mice to check the role of capsaicin. Oral glucose tolerance test and insulin tolerance test were conducted on mice after 12 h of fasting. Furthermore, an intestinal permeability test and short-chain fatty acids estimation were carried out to know the level of stored fat and glucose. Serotonin levels were also analyzed by HPLC. As a result, it was detected that capsaicin and mucin prevented high-fat diet-related complications. The weight of these mice was increased and higher glucose intolerance. Serum leptin levels were higher and increased metabolism. Serotonin and calcitonin levels were decreased in these mice. Gut microbiota was modulated by the intake of capsaicin.

2.7 Capsaicin protects against hepatic steatosis

Hypoestrogenic activity leads to abnormal deposition of fats and leads to different diseases including dyslipidemia, hypertension, fatty liver, inflammation, and oxidative stress. (Gong et al., 2022) explained Capsaicin and exercise have a combined effect against obesity. Its function is to increase insulin sensitivity and decrease calorie intake, abdominal fat, and body weight. Due to this, obesity-related complications are reduced preventing high blood pressure. The purpose of this study is to analyze the effects of capsaicin on arterial blood pressure and complications against dyslipidemia and hepatic steatosis. Capsaicin cream was developed by dissolving 15 mg of capsaicin in the cream. Animals were divided into 2 different groups HE which is fed with a normal diet and HEOb which was fed with a sucrose diet for 28 days. Cap cream was applied on the region which contain no hair or shaved abdominal skin. Blood pressure and biochemical profile were evaluated through a storage pressure meter. Biochemical profiles including high-density lipoprotein, low-density lipoprotein, triglycerides, and cholesterol are calculated. As a result, it was explained that elevation of calorie intake, abdominal fat accumulation, and body weight in HEOb-Sed rats. But capsaicin reduced body weight, lipid levels, and stored fat in the body.

2.8 Capsaicin prevents renal injury.

Acute renal injury is the loss of renal function, associated with organ failure and chronic kidney disease. Renal injury is also prevalent in most regions of the world Oxidative stress and mitochondrial dysfunction lead to acute renal injury. According to (Ran et al., 2022) Capsaicin ameliorated renal dysfunction and tubular cell injury. Capsaicin activates Nrf2 which improves mitochondrial integrity and defends the body against main different toxins. Renoprotective effects of capsaicin were observed. The purpose of this study was to evaluate the role of capsaicin against acute renal injury. Male mice were obtained which were knocked out by using mRNA. The blood of mice was analyzed with the help of cardiac puncture. Blood urea nitrogen and creatinine levels were determined. Further different analyses were also carried out to check the condition of the kidneys including measurement of ATP, and measurement of mitochondrial membrane potential. 0.3 mg of capsaicin was given to the mice including Iodixanol injection before intraperitoneal capsaicin injection. As a result, it was demonstrated that capsaicin protects against acute renal injury and kidney dysfunction by increasing tubular cell degeneration and tubular injury. Renal tubular cell apoptosis was also prevented by the administration of capsaicin in mice. A lower level of apoptosis-associated proteins was detected which reduced renal dysfunction. Oxidative stress in tubular cells was also prevented due to an increase in the intake of capsaicin. Mitochondrial dysfunction was ameliorated along with the knockdown of Nrf2. Thus capsaicin could be used as a therapeutic agent to protect against this problem.

2.9 Capsaicin protects against different types of cancer

Capsaicin has Antioxidants and anti-inflammatory effects so it helps to protect against several different types of cancers. According to (Han et al., 2022), it is explained that capsaicin help prevents lung cancer. Lung cancer is one of the leading causes of death in major regions of the world. Low sensitivity and drug resistance progress to lung cancer. Capsaicin inhibits the hypoxia-inducible factor which occurs in lung cancer. The hypoxia-inducible factor is a transcription factor that is involved in regulating cancer metabolism during oxygen deficiency. Under normal conditions, the hypoxia-inducible factor is degraded rapidly by the oxygen but in the abnormal state, it is present in the cells. Capsaicin increases the level of oxygen in the cell through mitochondrial respiration. ATP production is reduced to increase the level of oxygen in the cell. Multiple tasks were carried out by capsaicin in this condition including anti-obesity, antioxidant and anti-inflammatory. It generates apoptosis in cells which destroys cancer cells. A549, H1299, H2009, and H23 lung cancer cell lines are obtained from the body. These cells were treated with

capsaicin and incubated for 12h. Mitochondrial ATP production and oxygen consumption rate were measured. As a result, it was explained that cell growth and hypoxia-inducible factor were inhibited by capsaicin which caused lung cancer. Capsaicin caused the inactivation of hypoxia-inducible factors and protein accumulation. The hypoxia-inducible factor is inhibited by changing oxygen concentration in the cells. Mitochondrial ATP production was diminished to increase the levels of oxygen.

Another study by (Sánchez et al., 2022) explained the role of capsaicin in prostate cancer. It exerts antitumor effects on prostate cancer cells. It increases cell death in the prostate cancer cell lines and activates AMP-activated kinase. LKB1 phosphorylation was stimulated with the help of capsaicin and inhibited the cancerous cells from spreading. According to Sánchez et al., 2022 capsaicin reduces the risk of prostate cancer by inducing autophagy in cancerous cells. The growth and proliferation of prostate cancer cells were inhibited by administering capsaicin. This study was carried out to explore the role of capsaicin in the inhibition of prostate cancer cells. Capsaicin induces apoptosis and inhibits proliferation in cancer cells. Prostate cancer cell lines PC3, DU-145, and LNCaP were obtained in this case. These cell lines were grown in RPMI 1640 medium. Cell proliferation and apoptosis were analyzed through MTT assay and Annexin V-fluorescein isothiocyanate (FITC). As a result, it was analyzed that capsaicin inhibited prostate cancer cell proliferation. LKB1 was responsible for the activation of capsaicin AMPK. TRPV1 was required for the activity of capsaicin. TRPV1 has antitumor effects on prostate cancer cells.

2.10 Capsaicin increases locomotor activities and controls thermoregulation

Capsaicin increases locomotion and decreases the core body temperature. It is an effective Ligand for heat-sensitive transient receptor potential. According to (Inagaki et al., 2019). Capsaicin is capable of reducing shivering and generate hypothermia when it is administered in hypothalamus. Skin surface temperature is increased and colon temperature is decreased in rats.. So thermoregulation and locomotion were controlled by TRAP1 as shown in Figure 3. This study was carried out to investigate the effect of oral gavage of capsaicin on core temperature and locomotion activities. Adult male mice were obtained and they were deprived of food for 12 h. Oral gavage of stock solution of capsaicin was administered. Mice were divided into two groups. Core body temperature was measured under a 12 h light / dark cycle. The tail surface temperature was also calculated in the experimental animal. As a result, it was deduced that capsaicin induces a change in the core body temperature of mice. A significant increase in tail surface temperature was observed. The temperature was maintained by capsaicin in mice. Furthermore, long-lasting alteration in locomotion was observed. Higher locomotor activity was observed in these animals. Locomotion and temperature were balanced with the help of capsaicin so it regulates body mechanisms.

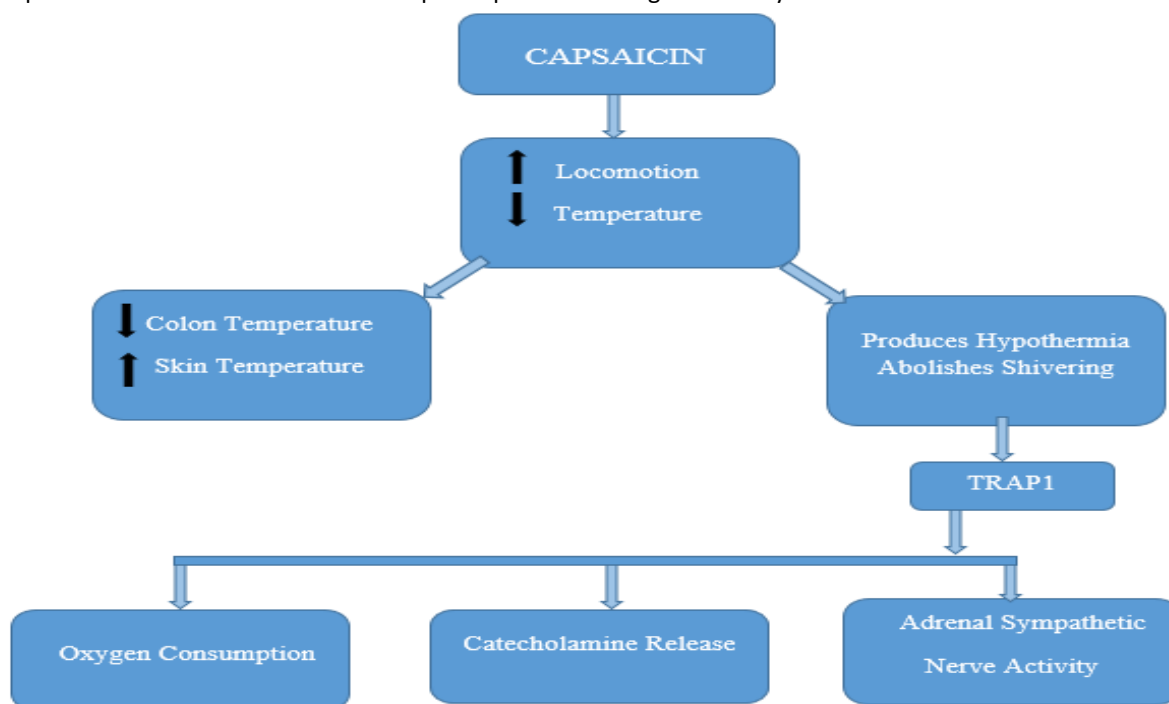


Figure 3: Thermoregulatory effects of capsaicin

3. Disadvantages of capsaicin

Capsaicin has a lot of potential health benefits, it can have negative side effects depending on the dose, administration route, and patient's sensibility. The major disadvantages and safety concerns related to the use of capsaicin are summarized in Table 2.

Table 2: Disadvantages of capsaicin

Subjects	Route of Exposure	Methodology	Findings	References
Humans	Oral (1 mg of capsaicin, 70 mg of cinnamaldehyde)	Double-blinded, randomized, cross-over, placebo-controlled	Peripheral thermoregulation high Cinnamaldehyde considered more tolerable solution compared to capsaicin	(Stephanie et al., 2016)
Mice	Orally by gavage	Divided into five groups (n = 10 per group): -NC group (normal control) -CAP group -LP. S58 group -β-glucan group -LP. S58 + β-glucan group	Quincke β-glucan coupled with β-glucan-utilizing LP. S58 relieved CAP-induced gastrointestinal injury.	(Tian et al., 2021)
Pepper samples	High performance Liquid Chromatography (HPLC)	76 pepper samples Black pepper (n = 40) Red pepper (n = 36)	Incidence of Aflatoxins contamination in red pepper in Iran was significantly higher than black pepper (p < .05)	(Afshin et al., 2016)
Humans	Topical route	Two groups (n=10 each group) CAP group Placebo Group	Capsaicin-induced central sensitization cause changes in ventral horn excitability outside of the targeted spinal cord segment, affecting efferent pathway outputs	(Valerie et al., 2021)
Rats	Orally administered	7–9 rats per group Control group UN-NAN group CAP group NAN group	Gastrointestinal injury model of rats showed that emulsions reduced the strong irritation of capsaicin.	(Jingjing et al., 2019)
Mice	Orally administered	Three groups (each group=7) K0=negative control K1=positive control	Capsaicin promotes the number of CD 34, angiogenesis factors, and	(Feri Setiawan et al., 2021)

		K2=treatment	microbial agents that it can be confirmed as the alternative treatment for bone defect healing caused by periodontitis.	
Humans	Orally administered	(31 females and 16 males; mean age: 25.0 ± 5.7 years; mean BMI: 21.5 ± 2.6 kg/m ²)	Oral burn caused by capsaicin affects thickness discrimination independently of reported chili pepper intake.	(Cong Lyu et al., 2021)
Humans	Topical	Single individual case report	Nine months after the application, neuropathic pain still remained and mobility difficulties in daily activities.	(Kilian et al., 2022)
Humans	Spray	Single individual case report	Oleoresin Capsicum Pepper Spray (OCPS) may induce Reversible Cerebral Vasoconstriction Syndrome (RCVS).	(Neeharika et al., 2021)
Humans	Spray	Emergency Department patients	A total of 1112 pepper spray-related injuries were identified, resulting in a national estimate of 34,582 pepper spray-related injuries	
Human	Orally administered	Single individual case report	RCVS should be considered in patients who present with severe headache after ingestion of ultra-spicy peppers	(Charolette et al., 2020)
Mice	Orally administered	6 independent groups (8 mice per group) a total of 48 mice	High dose chili extracts impaired gut permeability and induced gut dysbiosis but were attenuated by probiotics.	(Wimonrat et al., 2021)

Humans	Inhalation	Seventy-seven patients, with dry cough persisting for 3 or more weeks	Cough sensitivity is closely related with extra thoracic airway responsiveness during capsaicin provocation in some chronic cough patients.	(Sook Cho et al., 2019)
Humans	Topical	Twenty healthy participants aged 20–70 was randomly allocated to topical capsaicin or a placebo topical cream	Capsaicin-induced central sensitization may cause changes in ventral horn excitability outside of the targeted spinal cord segment, affecting efferent pathway outputs.	(Valerie et al., 2021)
Humans	Inhalation	21 subjects (all right-handed, 10 female)	Mechanical pain thresholds are lower in CAPS compared to CON	(Stefanie et al., 2020)

3.1 Capsaicin increases cough sensitivity in chronic cough patients

Intake of capsaicin increase the sensitivity in chronic cough patients. (Cho et al., 2002) explained the causes of chronic cough in patients which is elevated by consuming excess capsaicin. "Bronchial hyperresponsiveness (BHR), eosinophilic bronchial inflammation, or abnormal bronchial intraepithelial nerve are the major reasons for chronic cough in patients". The sensitivity of the extrathoracic cavity of the lungs was increased as the chronic cough take place. This study is carried out to evaluate the relationship between cough sensitivity and extrathoracic airway response on inhaling capsaicin. This explains the effects of capsaicin on the cough and respiratory tract in human beings. Patients were obtained who have chronic coughs of approximately 3 years. Chest radiographs were conducted to analyze the patients. A provocation test was conducted to determine the extrathoracic airway response and cough responsiveness. As a result, it was evaluated that capsaicin caused throat discomfort and epigastric soreness in patients with chronic cough. Coughing was also elevated in these patients which further progressed the disease.

3.2 Capsaicin leads to gastrointestinal injury

Capsaicin is a pungent ingredient and its consumption leads to gastrointestinal injury. According to (Tang et al., 2021), it was described that capsaicin results in many adverse events including abdominal cramps, and pain in healthy people. The gastrointestinal injury took place in rats after the administration of high doses of capsaicin. Capsaicin caused thinner intestinal walls, larger intestinal lumen, shorter villi length, and mucosal destruction. Many people experienced gastrointestinal discomfort after the consumption of capsaicin. This study was conducted to Qingke β -glucan combined with β -glucan could be a strategy to reduce GI injury. Rats were divided into 5 groups randomly and after 4 weeks feces of mice were gathered for different analyses. Morphology and pathology of the stomach and duodenum were analyzed. Serum parameters including levels of tumor necrosis factor, interleukin, interferon, somatostatin, and lipopolysaccharide were examined. PCR was used to extract the RNA of the stomach and duodenum. Gut microbiota was also analyzed in the fecal sample obtained from these mice. As a result, it was examined that Capsaicin reduced the weight of mice but administration of Beta-glucan improved the weight loss. Edema and ulceration of GI tissues were observed by the consumption of capsaicin. The weight of the stomach and small intestine was also increased in this aspect. Severe gastric mucosa erosion was seen. The gastric wall and glandular structure of mice were severely damaged by the consumption of capsaicin.

Another study was evaluated which explained capsaicin leads to gastrointestinal injury when it is consumed in excess amounts. According to (Han et al., 2020) peptic ulcers and gastroenteritis were caused by capsaicin due to which its use is limited. It causes gastric inflammation, inhibits gastric acid production, and causes structural changes in the intestinal barrier. Histopathological injury and tissue inflammation were observed after excess consumption of capsaicin. An emulsion of capsaicin was made in peanut oil of a ratio of 1:9 was prepared and concentrations of 0.5%, 1%, and 1.5% were obtained. 4 groups were made and each group contain 7 to 9 rats. These mice were fed for 2 weeks and after 24 h of treatment, rats fasted. Blood was obtained from the femoral artery and analyzed. The rat was slaughtered and gastrointestinal, kidney, lungs, spleen, and liver tissues were removed. These tissues were analyzed under the microscope and a serum index test was also carried out. Furthermore, antioxidant levels in gastrointestinal tissues and gastrointestinal inflammatory factors were determined. As a result, it was explained that the gastrointestinal injury model of rats showed that emulsions reduced strong irritation of capsaicin. Capsaicin damaged the mucosal tissue of the control group which didn't contain emulsions. Thus emulsions reduced gastrointestinal injury.

3.3 Capsaicin impaired gut permeability and induced gut dysbiosis

Capsaicin also helps to induce cell death mechanism in the body. Excess amounts of capsaicin can lead to diarrhea, loose stools, and dyspepsia. High doses are also responsible for cytotoxicity and activating inflammation. It can also reduce the number of probiotics present in the intestines of the human body. According to (Panpetch et al., 2021) it is stated that high doses of capsaicin can lead to severe health issues. It might affect the intestinal gut microbiota. The purpose of this study was to evaluate the role of *Lactobacillus rhamnosus* L34 (L34) and *Lactobacillus rhamnosus* GG (LGG) on the health condition of people. 6 independent groups of mice were made and each group contain eight mice. Mice were observed on daily basis and their weight and stool consistency was monitored after a short interval then various test were carried out. For further testing tissue and blood sample of mice was faced. Gut permeability and cytokines were also assessed. Pro-inflammatory cytokines were examined. As a result, it was deduced that it induces inflammation in the body. Body weight was also changed due to a change in fat proportion. Colon histological injury was present in these animals. Capsaicin-induced inflammatory cytokines destroy the cells and functions of the body.

3.4 Capsaicin cause reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome is a syndrome that is characterized by multiple disorders including cerebral edema, strokes, and thunderclap headache stroke. It is a type of vasoconstriction in the cerebral region along with nausea vomiting and severe headache. However intensity and frequency change over time. (Thottempudi et al., 2021) explained that excess consumption of capsaicin causes reversible cerebral vasoconstriction syndrome (Figure 3). This study was carried out to analyze a case after the use of oleoresin capsicum pepper spray. A 24-year-old medical officer visited who have no medical history previously. But she faced a thunderclap headache after being exposed to pepper spray. Neurological examination and angiogram of the neck and head were carried out to examine the symptoms. Headaches take place in different regions starting from the posterior neck region to the temporal region. Several other parts were also included in this headache such as bilateral and occipital regions. CT scan was carried out to analyze the abnormalities in the patients.

As a result, it was observed that pepper spray resulted in a narrowing of the middle cerebral arteries, anterior cerebral arteries, and bilateral posterior cerebral arteries. TRPV 1 causes stimulation of neurons and immediately releases some of the neuropeptides which constrict the arteries. Long-term exposure to capsaicin induces desensitization of neurons. Furthermore, capsaicin results in a narrowing of coronary arteries which decreases blood flow toward the heart. This component elevated heart rate and blood pressure.

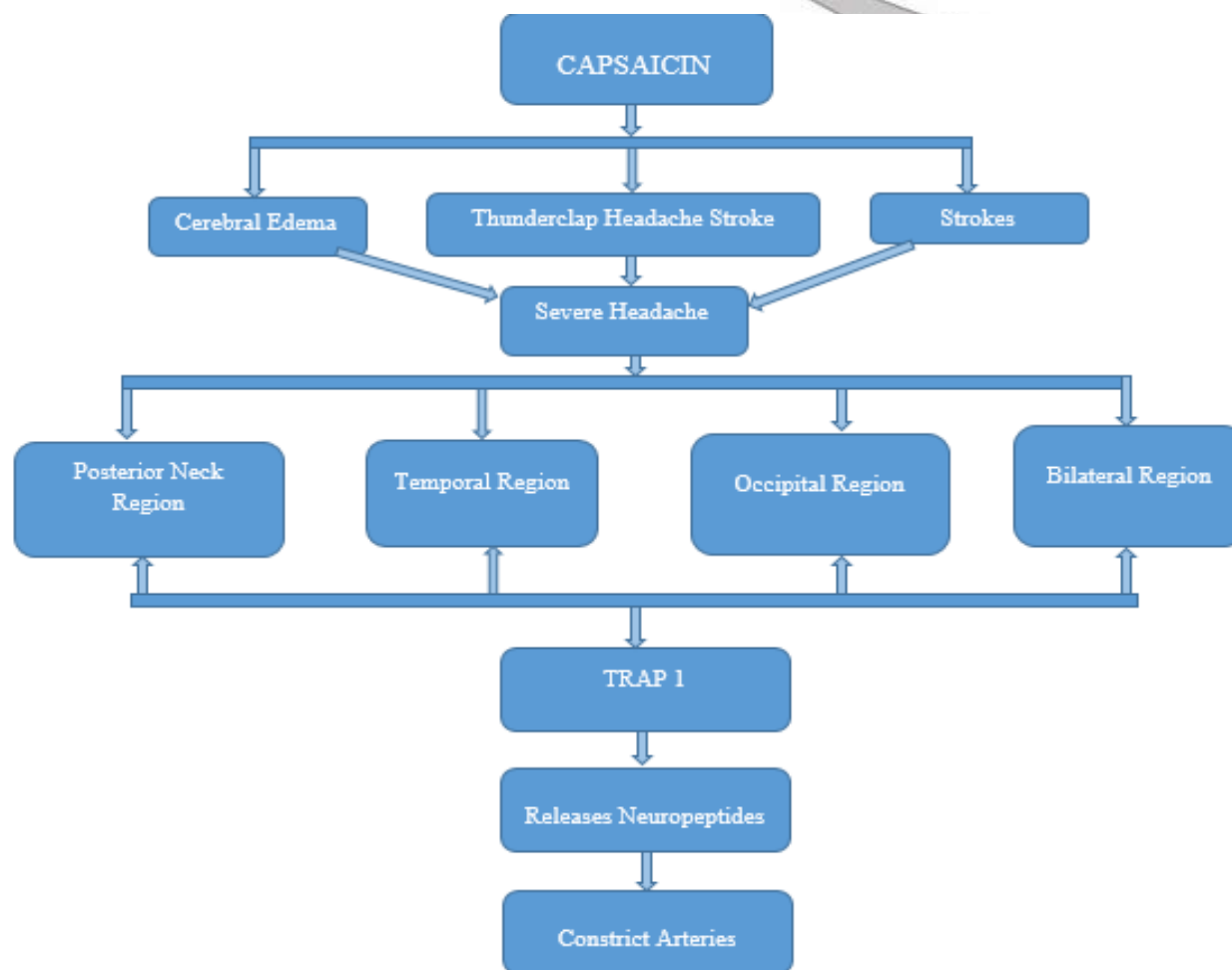


Figure 4: Capsaicin-Induced headache and vascular effects

3.5 Capsaicin causes pain and impacts the well-being of a human being

Capsaicin causes pain in the body as it becomes chemically sensitive and stressed. It activates trigeminal responses which cause painful burning and stinging sensations in the upper respiratory tract and eyes. This takes place with the help of receptors which are activated by many different irritants such as chemicals and toxins. In a study, (Heba et al., 2020) described painful sensations produced by an excess amount of capsaicin. The purpose of this study was to explain the neural connection of capsaicin and the reasons for these painful sensations. 21 participants were part of this study and these people have no psychological disorders. Capsaicin was administered through inhalation in these females. Thermal and mechanical testing was carried out along with an MRI of these patients. As a result, it was explained that thermal detection and pain threshold were similar. Mechanical pain was increased.

3.6 Aflatoxin contamination take place in capsaicin

Aflatoxin is a carcinogen that is present in contaminated red pepper containing capsaicin. Different types of aflatoxins were found including B1, B2, G1, and G2. According to (Barani et al., 2016) that contamination of peppers through aflatoxins could have severe side effects on the body. These aflatoxins are present in foodstuffs after the fungal contamination of substances. Many different diseases result in human beings after the consumption of aflatoxins in contaminated pepper. 76 samples of peppers were obtained including red peppers and black pepper. HPLC was carried out to analyze the number of aflatoxins present in each type of pepper. 50 g of sample was mixed with 200 ml of methanol, and 5 g of sodium chloride. HPLC was used for chromatic separation. Water and methanol were used as mobile phases to allow the separation of components. As a result, it was determined that samples of aflatoxins B1, B2, G1, and G2 were found. It was also determined that aflatoxins were present in higher

concentrations in red pepper as compared to black pepper. Several health risks were associated with the consumption of these aflatoxins.

3.7 Capsaicin causes central sensitization

According to (Evans et al., 2021) Central sensitisation is a disorder in which chain of neurological adaptation take place which cause amplification of nociceptors from non noxious and noxious sources.. Central sensitization is a state of neural hyperexcitability in the CNS. It effectively induced transient states of sensitization. Capsaicin caused an inhibitory effect on motor function and thus disrupts the functioning of the central nervous system. This study was carried out to examine whether capsaicin affects the motor functions and functions of the central nervous system. It is used to evaluate whether capsaicin-induced sensitization affects the functioning of the central nervous system. A change in the activity of motor neurons was observed by the administration of capsaicin. 20 healthy patients aged between 20- 70 were selected randomly. Tropical capsaicin cream was applied to the upper back of the male patients. To measure pain intensity and brush allodynia score, a visual analog scale was used. Intramuscular electromyography and surface electromyography was used to record motor unit activity. As a result, it was evaluated that a shift in the motor unit recruitment pattern was observed. A change in motor unit variability was observed after capsaicin is applied to the patients. Thus they may cause ventral horn excitability. Impairment of neuromuscular function also took place after the administration of capsaicin. Alterations in the movement patterns were observed in patients which influence sensitization.

3.8 Capsaicin causes a burning sensation in thickness discrimination

Capsaicin causes oral burning in the body. Capsaicin decreases taste intensity related to the sweetness of sucrose, bitter taste, and saltiness of salt. Capsaicin also affects the olfactory sensation and decreases smell intensity in human beings (Figure 4). According to (Lyu et al., 2021)it was explained that a burning sensation is produced by the consumption of excess chilies due to the presence of capsaicin. Capsaicin reacts with the gustatory system and causes loss of sensations. It can also shift the flavor and taste of food. In this study effect of oral burn on the thickness discrimination threshold of patients consuming spicy foods was evaluated. 47 participants were obtained in this study preference for chili peppers, spicy food intake and chili peppers intake was assessed through questionnaires. There were 6 questions related to the intake of chili peppers which helped to categorize the behaviors of the consumers.

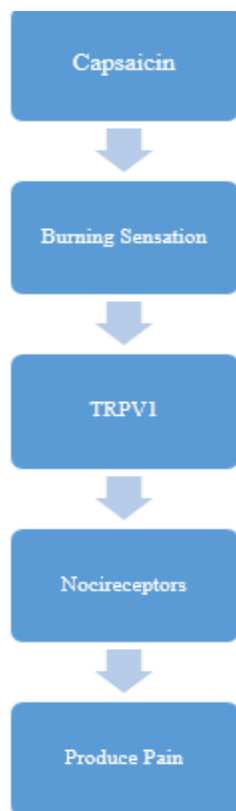


Figure 4: Capsaicin-Induced Pain Pathway

To determine the discrimination threshold for thickness 2-Alternative-Forced-Choice ascending staircase method was used. As a result, it was explained that discrimination threshold thickness was increased from 11.3 mPas to 16.1 mPas in all the participants. Oral burn caused by capsaicin has a positive effect on discrimination threshold thickness and alters the thickness. Thus burning sensation is produced by the intake of capsaicin.

3.9 High concentration of capsaicin causes second-degree burn

A burning sensation takes place after the administration of capsaicin. Capsaicin is a compound that causes a burning sensation when excess spicy food is consumed. It is due to the agonist action of TRPV1 located in the small diameter of sensory neurons. Nociceptors are activated by capsaicin which releases neuroactive peptides which trigger pain in that region. According to (Trin et al., 2022) capsaicin was involved in the burning sensation in the regions of the skin. This study was conducted to evaluate the problems which are caused by capsaicin. A 41-year-old woman undergoes surgery. Multiple surgeries of the patients initiated the pain. NSAIDs were not recommended initially and a skin patch containing capsaicin was placed on the wound. Firstly burning sensation was experienced by the patient and when the patch was removed erythema appeared under the skin. The patient was observed for 2 h and no assistance was provided. After a few hours, painful blisters appeared on the skin which caused difficulty in walking and many other problems.

4. Conclusion

Capsaicin is a biologically powerful phytochemical that plays a central role in the health effects of chili peppers through its interaction with the TRPV1 receptor. Evidence from recent experimental and clinical studies indicates that capsaicin offers substantial health benefits, including protection against metabolic disorders, inflammation, oxidative stress, organ injury, and certain cancers. Its ability to modulate lipid metabolism, immune responses, neuronal signaling, and mitochondrial function highlights its therapeutic potential in modern medicine. However, the same molecular mechanisms that underlie these benefits are also responsible for its adverse effects when consumed or applied in excessive amounts. Gastrointestinal damage, neurogenic inflammation, pain sensitization, vascular complications, and disruptions in gut microbiota demonstrate that capsaicin acts as a double-edged sword. Therefore, careful consideration of dosage, formulation, and individual susceptibility is essential for safe and effective use. Future research should focus on optimizing delivery systems, defining safe therapeutic windows, and further elucidating TRPV1-mediated pathways to maximize the benefits of capsaicin while minimizing its risks.

Author's Contributions

Ammara Mujahid: Conceptualization and Writing – original draft preparation.

Abdurrauf Azam: Data curation and Methodology

Nasir Islam: Formal analysis and Visualization

Bushra Murtaza Malik: Software and Writing- Original Draft.

Awais Raza: Supervision, Overall project administration, Validation

Ahmed Bilal: Investigation and Writing – review and editing.

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All authors agree to publish.

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