CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.3376280

Available online at: http://www.iajps.com *Research Article*

CAPSAICIN – BENEFICIAL EFFECT OF ORIENTAL SPICE ON SKIN, HEART AND CANCER CELLS

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Article Received: Dec 2018 **Accepted:** July 2019 **Published:** August 2019

Abstract:

Capsaicin is known as the primary pungent principle in Capsicum fruits. It is a compound found in chilli peppers that are massively consumed spices throughout the world. Capsaicin is a highly selective agonist for TRPV1 (transient receptor potential cation channel, subfamily V, member 1) receptor. TRPV1 is essential in reducing oxidative stress, inflammation and pain sensations. Thus, it has many pros related to health issues. The positive impact of TRPV1 and its activation via capsaicin has been studied in cardiovascular diseases, various cancers, dermatological conditions, diabetes, and obesity and many other health-related problems. With the help of previous experimental studies, capsaicin improves the heart health by reducing high blood pressure, high cholesterol levels and many other heart-related diseased complications. The TRPV1 also plays a major role in skin health as the capsaicin receptor is present in nociceptive nerve fibres and non-neural structures. It stimulates the release of a compound that is involved in communicating pain between the spinal cord nerves and other parts of the body. This review article will add growing evidence for the beneficial role of capsaicin and TRPV1 helps to lower the risk of cardiovascular diseases and conditions related to skin diseases.

Key Words: *Capsaicin, TRPV1 Receptor, Heart Health, Skin Health*

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Please cite this article in press Shahnai Basharat et al., ***Capsaicin – Beneficial Effect Of Oriental Spice On Skin, Heart And Cancer Cells.,*** *Indo Am. J. P. Sci, 2019; 06[08].*

INTRODUCTION:

Capsaicin, an active ingredient of chilli peppers,[1] is obtained from the plants of genus Capsicum,[2] which is the most massively consumed chilli in the world. It is included in a chemical group known as capsaicinoids. Capsaicin is responsible for the pungent quality flavour in chillies .[3]

Composition: Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide)[4] is a naturally occurring alkaloid derived from chilli pepper fruit. It is obtained from plants of the genus Capsicum. Its molecular formula for capsaicin is C18H27NO3.[5] it is easily evaporated, odourless and colourless white crystalline powder. Capsaicin is synthesized in the chilli pepper by addition of a branched-chain fatty acid to vanillylamine.[6]

Health Benefits: It is utilized for the treatment of inflammatory disorders such as psoriasis, brachioradial pruritus, aquagenic pruritus, notalgiaparasthetica, nodular prurigo, and pruritus produced in patients on hemodialysis.[7] Dietary capsaicin had a beneficial metabolic impact on genetically diabetes[8] as it helps in reducing plasma levels of glucose, insulin and triglycerides, eventually regulating the glucose level through hormone called adiponectin.[9] The impact of capsaicin on fat digestion also show the capacity to lower serum and liver cholesterol levels.[10]

Capsaicin about CVD and Hypertension: Cardio-Vascular Diseases (CVD) is a set of ailments of the heart and veins that incorporate hypertension, coronary heart diseases, cerebrovascular sickness, heart failure, peripheral vascular disease, and so on.[11]

Red chilli pepper constituent "capsaicin" could reduce total cholesterol[12], triglyceride, and low-density lipoproteins and raises high-density lipoproteins level.[13] The cardiovascular system is enriched in capsaicin-sensory nerves that assume an essential role in managing cardiovascular capacity through the release of epinephrine, for example, CGRP and substance P. CGRP is viewed as the most intense vasodilators and assumes a critical role in controlling pulse under both physiological and pathophysiological conditions. Capsaicin animate the arrival of CGRP through the stimulation of TRPV1 and in this pattern lessens the blood pressure.[14]

Hypertension is related with blood vessel hardening, and conservative thoughts propose that hypertension quickens aortic altering and hardening, moreover vascular smooth muscle cell hypertrophy, as a versatile procedure to expand divider to-lumen width proportion because of long-lasting changes in hemodynamic forces.[15] Hypertension is a critical worldwide public health issue with high recurrence. The quantity of grown-ups with hypertension is evaluated to increment to an aggregate of 1.56 billion of every 2025.[16]

Dietary capsaicin improves stress overload incited cardiac hypertrophy. Also, the antihypertrophic activity of capsaicin is relying on TRPV1 channels. These conclusions showed that there is another critical process working for the hypertrophy, or, in other words, the TRPV1 channels, bringing about an expansion of intracellular calcium concentration that consequently activated many cell processes.[17]Furthermore, initiation of TRPV1 by capsaicin obstructs foam cell arrangement by instigating autophagy in oxidized low-density lipoprotein treated vascular smooth muscle cells and at last, impedes the procedure of atherosclerosis.[18] Each 1-mg/dL increase in HDL-C levels is identified with decreases of 2– 3% in CVD hazard.[19] It lessens the chances of atherosclerosis and stroke by improving endothelial capacity.[9]

These findings additionally promote the potential clinical estimation of capsaicin on the inhibition of cardiovascular maladies, for example, atherosclerosis and coronary illness. Besides this, it has been stated that the general utilization of chilli for about a month builds the opposition of serum lipoproteins to oxidation in adults.[14]

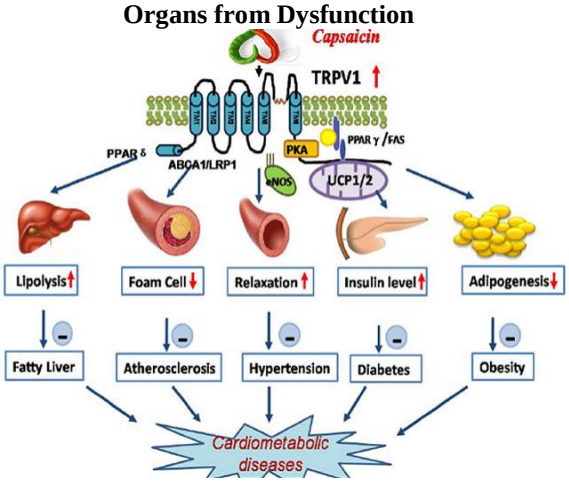
Capsaicin about Skin: In the skin, TRPV1 is shown either by neural or by non-neural structures.[20] When TRPV1 is activated, it helps to induce calcium influx in the epidermal keratinocytes, which eventually reduces inflammatory response from harmful cutaneous stimulation. Capsaicin has two phases effect; initial phase leading to desensitisation. Initially, capsaicin activation of TRPV1 on nociceptive nerve endings leads to the transmission of these signals to the nervous system which results in inducing a burning sensation. As the administration of capsaicin is repeated, all these effects are followed by a reversible defunctionalisation of nociceptive sensory nerve fibers.[21] The outcome lessens the local pain and a reduction of hyperesthesia to mechanical and heat stimuli. This suggests that in order to help in chronic pain syndrome, capsaicin is used as a peripheral analgesic. In chronic inflammatory skin diseases, capsaicin treatment helps to minimize the neurogenic inflammation.[22] Capsaicin is also beneficial for the treatment of the psoriatic disorder, pain induced by musculoskeletal disorders[23], and neuropathic pain. Capsaicin creams are developed with property to lessen the effect of inflammation and itching.[24] Repeated doses of Capsaicin has shown to lead to "defunctionalization" of the nerve and long-term reduction of pain.[25]

In the Skin, Capsaicin binds to nociceptors, which leads to initial excitation of the neurons and enhanced sensitivity to noxious stimuli, usually perceived as burning sensation and itching.[26]

Review of Literature:

Capsaicin and Heart Heath:

Dietary Capsaicin Protects Cardio Metabolic Organs from Dysfunction



The figure reflects the effects of capsaicin on cardiometabolic disease or any relevant organ damage. It shows how dietary capsaicin activates TRPV1, which regulates glucose and lipid metabolism and also control vascular function. It also promotes the breakdown of fats through the activation of Peroxisome proliferator-activated receptors, simply known as PPAR. It also boosts the dilatation of blood vessels, which decreases blood pressure through increasing eNOS expression. It also manages the insulin level by PKA activation. It also strict the formation of foam cell via controlling ATP-binding cassette transporter (ABCA1) and LRP1.

Moreover, by activating PPAR, it also eliminates adipogenesis. Thus, dietary capsaicin helps to reduce fatty liver, hardening of the arteries, high blood pressure, diabetes and obesity. The figure proves that it likely contains the beneficiary elements for cardio diseases in overall population.[27]

Protective Mechanism of Capsaicin with the help of previous studies:

Cardiac Hypertrophy: In 2014, Feng Gao et al. conducted a study to observe a high salt diet leads to either cardiac hypertrophy or fibrosis. These both are related to the rise in reactive oxygen species creation. Transient receptor potential vanilloid type 1, simply known as TRPV1, which is a specific receptor for capsaicin, holds the protective role in the cardiac regimen. Feng Gao and his colleagues took two groups of mice. One group contains wild type mice, and other has TRPV1-null mice. They grouped the mice randomly. Mice were nourished with a normal salt diet which contained about 5% NaCl, high salt diet containing 8% NaCl and high salt plus capsaicin contain 8% NaCl plus 0.01% capsaicin by weight for 1 year. These modifications were linked with down-regulation of proliferation activated receptors δ, UCP2 expression and improved oxidative/nitrotyrosine stress. Long term high-salt diet shown reduction done in chronic treatment with capsaicin. H9c2 cells and cardiac tissue slides from WT mice were stable with 10% formalin at room temperature for 60min. After that, they were bathed in a 2% hydrogen peroxide methanol solution for about 30min. The cells were cherished at 4∘C and incubated at room temperature for a period of 30min. The above arrangement proposes that intake of dietary capsaicin lessens the long term high salt diet that brings out cardiac hypertrophy and also fibrosis. This beneficial effect occurs due to TRPV1 mediated up a settlement of PPAR-δ expression. UCP2 plays basic role in ROS detoxification. This study also proved that UCP2 in left ventricular restored after the activation of TRPV1 in the high salt group. It also verified that the UCP2 expression is linked to the shielding role of TRPV1 in the myocardium. This effect plays a vital role in the heart as it guards against oxidative stress induced myocardium damage.[28]

In 2014, Qiang Wang et al., proved that the dietary capsaicin leads to the betterment in many heart-related diseases including high blood pressure, atherosclerosis, glycaemia and dyslipidemia. This study was conducted to examine the capsaicin role in cardiac hypertrophy and fibrosis in a pressure overload model. Sham and aortic banding surgery groups were made randomly. Moreover, divided TRPV1 knockout mice and wild type littermates into these group. To make Male mice unconscious, intraperitoneal injection of pentobarbital (50 mg/kg of body weight) was given. These mice aged 8 weeks. Adrenal AB Surgery was performed. The similar procedure was done for sham surgery without band placement. Three days after AB surgery was done, mice were given the normal standard chow (control group) and normal chow plus 0.01% capsaicin (capsaicin group). The hearts of the mice were harvested after ten weeks of surgery, then the heart weight/body weight and also the left ventricular weight/body weight ratio were properly checked. After this specific period, the outcomes showed that dietary capsaicin weakens the pressure increased heart weight index, ventricular volume enlargement. It also showed a reduction in the function of cardiac hypertrophy in WT mice. However, TRPV1 KO mice did not show any effects. The results prove that capsaicin has a beneficial and protective role in cardiac response and shows that how it protects against cardiac hypertrophy.[17]

Atherosclerosis: Kuo-Shuen Chen et al., evaluate the anti-oxidative movement of capsaicin in 2015. In this study, the component was decided by which capsaicin saves human umbilical vein endothelial cells from oxLDL mediated dysfunction. Capsaicin has many health-promoting properties, which include anti-oxidant, anti-inflammatory, anti-cancer, and also lowers the level of lipid. According to the ongoing investigation, capsaicin can slow down the ApoB fragmentation and also the development of conjugated dienes in LDL, which is proposed by copper. This information proposes that capsaicin showed the antioxidative capacity to decrease LDL oxidation. Hence, the protection of capsaicin against oxLDL-prompted endothelial dysfunction can be associated with suppression of ROS excess production. The results prove that the defensive mechanism of capsaicin against the cellular oxidative stress on HUVECs. Capsaicin can easily secured cell arrangement in macrophages RAW 264.7. All these cells were treated with local LDL or oxLDL in the presence of capsaicin (10, 20, 30, 40, and 50 lM) or not for 24h. The outcome proposed that capsaicin prevents oxLDL from initiated cellular dysfunction. Also, that capsaicin exhibited protective effects or mechanism against cellular oxidative stress. This study also cleared the doubt with the help of Western bolt examination that capsaicin helps against Lipopolysaccharide causing inflammation in RAW 264.7.[29]

Coronary Heart Disease: If the level of HDL is less in amount, then it leads to more chances of having heart disease like coronary heart disease. To explore the health benefits of capsaicin, which helps balance the amount of HDL. The study was done by Yu Qin et al., in 2017. This study was done in people with age group between 18 and 35. The trial was randomized, double-blind and controlled clinical. 42 volunteers were selected which were taken in between June 2014 and December 2014. They were randomly divided into capsaicin and the control group. Capsaicin dose was given to both the group daily, two times a day for at least 3 months, but the doses of capsaicin were 4 mg in the capsaicin group and 0.05 mg in the control groups. In this time duration, the diagnostic results were almost the same in both. However, some showed different outcomes like fasting serum HDL-C levels sufficiently become greater in amount.4 mg of capsaicin was given daily for about three months. After this period, there was an increased level of fasting serum HDL-C and anti-inflammation in adults with low HDL-C.

In conclusion, capsaicin improved risk factors of CHD in individuals with low HDL-C. It also showed that it could play a role in treating and preventing CHD. The data showed that every 1-mg/dL improvement in HDL-C levels could reduce 2–3% in CVD risk.[19]

Myocardial Infarction: TRPV1 puts cellular reaction to pain, heat, or harmful stimuli by calcium influx. However, the task of TRPV1 in the heart muscle is unknown. Capsaicin, the specific TRPV1 agonist, decreases mitochondrial membrane. The study was Supervise by Carl M. Hurt in 2016 to find an interaction site for TRPV1 with calcineurin. Hemodynamic outcomes for exploratory groups was calculated at baseline for around 15 minutes of ischemia, and at 2 hours of reoxygenation injury. Male Sprague-Dawley rats aged 8 to 10 weeks and TRPV1 knockout rats were used for the studies outlined. For further investigations, Peptides were synthesized using microwave chemistry and named as peptides V1-Cal and A5-Cal. In vivo rat heart attack, V1-cal can reduce the Heart attack risk. The size reduction of infarct by V1-cal was not seen in TRPV1 rats. Both V1-cal and A5-cal were given at doses of 1 mmol/L for 10 minutes. So it was concluded that the V1-cal mostly reduces injury by preventing the relation of calcineurin with TRPV1and As shown by the study, capsaicin has a small therapeutic window for cardioprotection that increases heart rate which can be helpful in acute myocardial infarction. The Data recommends that TRPV1 is an end-effector for Heart protection.[30]

According to Huan He study which was conducted in 2017, it has been shown that application of Cap reduces the myocardial injury due to I/R in rats. Therefore, the main purpose of this study was to check either SIRT1 (sirtuin) interfere with the shielding effects of Cap against cardiomyocytes damage. The test was done on the neonatal rat. Cardiomyocytes were taken from 2-day-old Sprague Dawley rats. The cells were harvested after centrifugation (5 min, 60) and were washed after 18 hours and were then cultured for 2 days. After which it was given exposure of anoxia and then incubated in the chamber for 4 hours. After separating cells from anoxia medium, they were incubated for two hours. While the cells were incubated for six hours with the fresh culture growth medium. Using Cap (from 10 μM to 40μM) or Cap (20 μM) plus Sirtinol (60 μM), cells were cultured. The Capsaicin boosts the level of cell viability, making a clear rise in the expression of SIRT1 and Bcl-2. The control group had more increase in cell viability than the A/R group with the optimal concentration of Cap kept as 20 μM. The outcome was increased in the level of activities of LDH and CPK in the A/R group when compared with the control group. This confirmed that Cap could protect cardiomyocytes from damage caused

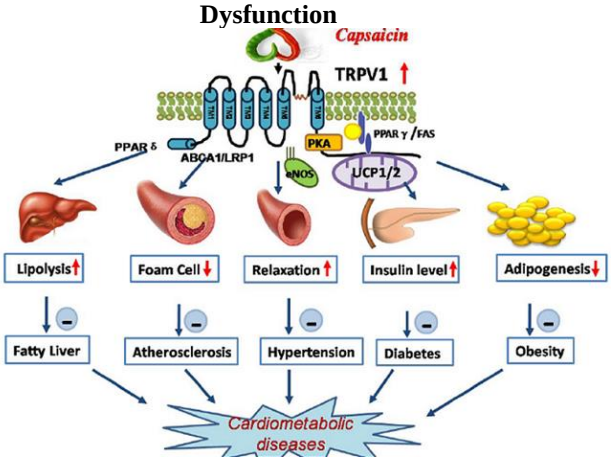
by A/R and that SIRT1 was involved with those cardiomyocytes.[31]

Cardio toxicity: The research was conducted by Mihir K. Patel and Anita A. Mehta in 2016, which aim was to focus on the beneficial effect of capsaicin on acute doxorubicin-induced cardiotoxicity in mice and its possible role of oxidative stress. Doxorubicin (DXR) is used for different kinds of cancers, including breast cancer, leukaemia and sarcoma. However, its use is not beneficial to the heart as it can cause cardio toxicity, which is a major risk factor in heart failure. Capsaicin being the antioxidant helps in reducing oxidative stress. So the basic agenda of this study is about capsaicin and its role in cardiovascular diseases using different kinds of methods and test. These tests include biochemical and histopathological ways. This study was done on albino mice, which were 25-30g and lasted for 10 days. All kinds of treatment were done on all the 6 groups, all containing 6 mice. DMSO (Dimethyl sulfoxide) with the addition of capsaicin and saline was made. Groups with DXR treatment showed an increased level of cardiotoxicity, i.e. serum CK-MB, LDH and tissue MDA. Also, it showed less level of antioxidants.

On the other hand, mice with capsaicin (1mg/kg) treatment showed elevated levels of antioxidants, fewer toxins and histopathological results proved less damage to heart cells and more healing due to capsaicin effect. On the 11th day, the outcome showed that mice with capsaicin treatment were healthier and that it protects the heart by an antioxidant mechanism. This study proved the positive effect of capsaicin on cardiotoxicity due to its antioxidant's nature in mice.[32]

Capsaicin and Skin Health:

Dietary Capsaicin Protects Skin from Dysfunction



The capsaicin-induced inflammatory response is proposed through the activation of TRPV1. This activation causes the nerve endings to release pro-inflammatory neuropeptides. Substance P (SP) and calcitonin-gene related peptide (CGRP) are known as the most important neuropeptides; they both are activated by CGRP receptors and neurokinin-1. As a result, they lessen the dilation of vessels and are responsible for the rise in vascular permeability. Neuropeptides which are released encourages degranulation of mast cell. It increases the volume of capsaicin-induced neurogenic inflammation.[33]

Psoriasis: Psoriasis is a T-lymphocyte-mediated autoimmune skin disorder affecting the epidermis and dermis. It commonly causes red patches with silvery white scales. Ruchi Gupta et al., in 2015, investigated to evaluate the potential of capsaicin to improve its tropical delivery for an effective therapy for psoriasis. The Capsaicin contains liposomes, emulsions and niosomes. Liposomes containing CAP were prepared by the thin-film hydration method while CAP-loaded emulsomes were prepared using the film hydration method. The study was held comparative between them through in vitro and in vivo parameters. In vivo, the dialysis tube for a period of 24h was used while the Franz diffusion cell was used in vitro. Cap percentage, which accumulated into the skin, were noted down at the end of the experiments. The study showed that Cap loaded in the vesicle-based gel as carriers play a vital role in the treatment of psoriasis. The results also proved to increase therapeutic efficacy.[34]

Oedema: A research was conducted by Khomendra Kumar Sarwa et al in 2014. A formulation of topical ethosomal in capsaicin was made. Capsaicin was introduced as a significant spiced flavour in chilli pepper, and evaluation was done for arthritic rats. Capsaicin is also known for inducing pain signals to the brain. It causes less pain signals to the brain attempting into fake or temporary pain. This procedure leads the neurons of the brain to induce less pain and long lasting relief. This is also used in the form of injections to relieve pain. However, some patients reported better results when injected orally. The Capsaicin (capsaicin 95% USP) used in the study contains capsaicin (59.87%), dihydrocapsaicin (34.75%) and no hydro capsaicin (3.21%). Capsaicin was prepared in Nano injected form to test on adult male Wister albino rats. There were 4 groups, each containing 6 rats. A vessel was specially designed used in which capsaicin (0.05%) and phospholipid (2%) was added to make the mixture using a sonicator. For topical use, ethosomal carrier encapsulated with the addition of capsaicin was made. Similarly, the same methods were used to prepare empty ethosomes but without the addition of capsaicin. This study was planned for 28 days. The injected capsaicin proved to be better than gel-form capsaicin. No skin allergies were observed

during these tests. From these results, it was concluded that topical ethosomal capsaicin could be used in the treatment of long term arthritis and muscle disorders which include inflammation and skeletal disorders.[26]

Skin Permeation: In 2014, Jee Hye Kim et al, conducted a study on Preparation of a Capsaicin-Loaded Nanoemulsion for Improving Skin Penetration. Capsaicin oil in water Nanoemulsions with enhanced skin permeation was successfully done. The study was done to explore the optimum condition of capsaicin-loaded. The oil phase was oleoresin capsicum, and the aqueous phase was used. Oleoresin capsicum contains 22.67 mg/g of capsaicin, which is an oil-soluble ingredient. The surfactants were used was nonionic, Tween 80 and Span 80. These mixtures were used with distilled water, which was stirred for 30min and at 75 °C. To check the right proportion of surfactant blend, the Hydrophile-Lipophile balance (HLB) estimation of surfactant was done. Surfactants having higher HBL values made more stable oil in water emulsion than those with lower HLB values. That's why HLB values ranging from 9 to 15 were chosen to cover optimum condition. The capsaicin content was then evaluated through a reverse phase of HPLC. The result proves that the capsaicin-loaded Nanoemulsions have a promising effect as a transdermal delivery carrier. It shows effects in all types of skins for the proper penetration.[35]

Skin Inflammation: According to Pinaki R. Desai et al., a study which was conducted in 2013. The objective of this study was to design and also evaluate the therapeutic efficacy of anti-nociception agent Capsaicin against chronic skin inflammatory diseases. Two types of rats were taken; Hairless rats (350–400 g; male) and other were C57BL/6 mice (6 weeks old; male). The mice were fed and were allowed to drink water as much as they wanted to. Novel carrier system was designed for delivering anti-inflammatory agents siTNFα and Cap into the deep dermal milieu. Therapeutic efficacies of CyLiPns was seen using a model which was like the imiquimod-induced psoriatic plaque. It carried both Cap and siTNFα. 2.5 mg of Cap was used in order to make Cap encapsulated nanoparticles (C-CyLiPn) and was dissolved in PLGA organic phase. Also, siTNFα with CyLiPn (S-CyLiPn) was prepared in aqueous solution. A mix of Cap and siTNFα encapsulated CyLiPn (CS-CyLiPn) was also made the addition of siTNFα in an aqueous phase and Cap in an organic phase. For 5 days, test formulations were used on inflamed skin. All the findings supported that normal carrier nanoparticles can easily carry siTNFα and Cap into wide dermal sites. Moreover, the results proved that Cap, along with the combination of siTNFα, can treat inflamed skin. Also, it was shocking how the amount of Cap form CyLiPn was much higher than the capsaicin market available creams.[36]

Pain Amplification Syndrome: Florian Henrich et al., conducted the study on Capsaicin-sensitive C- and A-fiber nociceptors control long-term potentiation-like pain amplification in humans. This study was conducted in 2015, and only male's volunteers were taken, which were about thirty-five. Two experiments were performed, one with LTP (long-term potential) induction in capsaicin-desensitized skin in which 23 volunteers participated and one with LTP induction in which 15 volunteers were enrolled. 2 volunteers participated in both experiments. 8% capsaicin patch was used for 2 to 22 h. Both the experiments were done with a 4 month gap. The experiment was based on two selective nerve block.

The findings showed that TRPV1-antagonists plays a potential role in the prevention of pain from going acute to a chronic condition. This happened due to heterotopic LTP. Also due to capsaicin patch, the pain was reduced by 71% compared to the other site.[37]

CONCLUSION:

Chilli peppers no longer belong in the kitchen only. They are now being used as the latest form of medicine. It is considered to help in weight loss, increasing HDL level, to fight against cancer and even chronic pain etc. Capsaicin belongs to the family known as the vanilloid family. TRPV1 is a receptor on which the capsaicin binds and performs its function. Physical abrasion, heat, and also proton help capsaicin to stimulate. When the capsaicin activates, it allows cations to pass through the membrane of the cell. Loss of poles of neurons occurs as a result which stimulates and then the signal is transferred to the brain. After binding, the molecule of capsaicin produces exactly the same sensations like those of excessive heat damage. Due to this reason, the spiciness of capsaicin is felt as a burning sensation.

Table: 1 Original Research

DietaryElement	Subjects	Duration	Effect	Reference
A high salt diet with Capsaicin 0.01% NaCl 8%	Two groups; Wild-type mice & TRPV1 mice	1 Year	Lessen the risk of cardiac hypertrophy and fibrosis	Gao F et al.,[28]
Normal chow plus 0.01% capsaicin	Two groups; TRPV1 knockout mice & wild type littermates (only males was taken)	Ten weeks	Protects against hypertrophy	Wang Q et al.,[17]
Capsaicin 10,20,30,40 and 50IM	Macrophage Raw 264.7	24 hours	Prevents oxLDL initiated cellular dysfunction, protective effects against cellular oxidative stress	Chen KS et al.,[29]
V1-cal dose & A5-cal 1mol/L	Two groups; Male Sprague-Dawley rats & TRPV1 knockout rats	10 minutes	Cardioprotection effect increases heart rate which helps in acute myocardial infarction	Hunt C et al.,[30]
Capsaicin 1mg/kg	Albino mice (25-30g)	Ten days	Elevates the level of antioxidants and protects the heart	Patel M et al.,[32]
Capsaicin	Rats	24 hours	Cap loaded in vesicle-based gel treats psoriasis	Gupta R et al.,[34]
Capsaicin 95% USP	Male Wistar albino rats	28 days	Treats long-term arthritis, inflammation	Kumar SK et al.,[26]
2.5 mg of cap	Two types; Hairless rats & C57BL/6 mice	Five days	Cap with siTNFα treats inflamed skin	Desai PR et al.,[36]
8% capsaicin patch	35 (only male)	2 to 22 hr	Pain is reduced from going acute to chronic	Henrich F et al.,[37]
Capsaicin 22.67% mg/g	Nanoemulsion	30 min	Helps in all type of skin for proper penetration	Kim JH et al.,[35]

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