ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 7, 2022

Online - 2455-3891
Print - 0974-2441

Review Article

THERAPEUTIC PROPERTIES OF CAPSAICIN: A MEDICINALLY IMPORTANT BIO-ACTIVE CONSTITUENT OF CHILLI PEPPER

SANGRAM SINGH[1]*, MOIN UDDIN[2], M. MASROOR A. KHAN[1], SARIKA SINGH[1], AMAN SOBIA CHISHTI[1], UROOJ HASSAN BHAT[1]

[1]Department of Botany, Faculty of Life Sciences, Aligarh Muslim University, Aligarh, Uttar Pradesh, India. [2]Botany Section, Women's College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India. Email: sangramsinghbachchan@gmail.com

Received: 12 February 2022, Revised and Accepted: 10 May 2022

ABSTRACT

Plants are the source of numerous pharmaceutically important compounds that have been employed to cure various human ailments since ancient times. With the assistance of modern chemistry and materials science, such pharmaceutically important compounds have been identified and isolated to produce new drugs. Alkaloids are one of the most significant classes of naturally occurring secondary-metabolites, which are synthesized and widely distributed in various parts of plants. They regulate various metabolic activities and induce physiological responses in the human body. Capsaicin is a naturally occurring alkaloid found in many species of peppers and is attributed to their spicy nature and pungent flavor. This alkaloid is a member of the Capsaicinoids group, which includes capsaicin, homocapsaicin, homodihydrocapsaicin, dihydrocapsaicin, and nordihydrocapsaicin. Capsaicin has a wide range of therapeutic potential against various human ailments. In this article, we provide a comprehensive overview of the capsaicin molecule as well as an examination of its medicinal properties in a variety of human disorders, including pain, various types of cancer, ulcers, diabetes, obesity, inflammation, cardiovascular diseases, and neurodegenerative diseases.

Keywords: Alkaloids, Capsaicin, Capsaicinoids, Pharmacological, Therapeutic.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i7.44405. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Plants are the major source of pharmaceutically important active compounds, with so many medicines derived directly or indirectly from plants. Plants make major contributions to the prevention and treatment of diseases, accounting for nearly 25% of pharmaceuticals prescribed worldwide that are derived from plants. 121 such active phytochemicals are now in use, with 11% of the WHO's 252 basic and essential medicines being derived only from flowering plants [1,2].

Plants and plant-derived active constituents have a long track record of being utilized to cure a wide range of ailments with improved patient acceptance and tolerance. At present, about 35,000–70,000 species of plants have been evaluated for their therapeutic potential. Morphine was the very first plant-derived natural compound, while aspirin was the first semi-synthetic pure drug that was introduced and commercialized for therapeutic use. This increased the identification and isolation of several pharmaceutical active compounds, including atropine from *Atropa belladonna*, quinine and quinidine from *Cinchona* spp., digoxin from *Digitalis* spp., codeine from *Papaver somniferum*, and vincristine and vinblastine from *Catharanthus roseus*. The vast majority of these drugs cannot yet be commercially manufactured and must, therefore, be derived from wild-or cultivated-plants [3].

Artemisinin, derived from the Chinese herb *Artemisia annua*, is used in the treatment of multidrug-resistant malaria. Silymarin, which is extracted from the seeds of the *Silybum marianum* plant, is used to treat liver issues. Paclitaxel, derived from *Taxus brevifolia*, is used in the treatment of a variety of malignancies, including lung, ovarian, and breast cancer. These are just a few examples of plant-derived compounds that have been synthesized and commercialized as pharmaceuticals in recent years [1].

Through increased insights into medical science and clinical observations, there is indestructible evidence suggesting that existing plant-derived compounds are finding new applications. For example, forskolin, an alkaloid derived from *Coleus forskohlii* and an active phytochemical from *Stephania glabra*, has been recognized as an adenylate cyclase and nitric oxide stimulator, which might minimize the risk of obesity-related complications and atherosclerosis problems [1]. Several plant-derived drugs have been introduced during the last two decades. For example, Nitisinone, developed from the natural compound Leptospermone (*Callistemon citrinus*), is used in the treatment of tyrosinemia, and the semi-synthetic compound apomorphine, derived from morphine, is used for the treatment of Parkinson's disease. Similarly, tiotropium, a derivative of atropine obtained from *Atropa belladonna*, is often used in the treatment of cardiovascular disorders. In the same way, artemether, an endoperoxide sesquiterpene lactone and semisynthetic compound derived from Artemisinin, is used to treat malaria, and Dronabinol and Cannabidiol, obtained from the Cannabis plant (*Cannabis sativa*), and capsaicin, obtained from *Capsicum annuum*, are used as pain relievers [1].

ALKALOIDS

Alkaloids are nitrogen-containing secondary metabolites of plants that are synthesized and widely distributed in the leaves (*Hyoscyamus niger*), stem bark (*Cinchona officinalis*), roots (*Rauwolfia serpentina*), and fruits (*Strychnos nux-vomica*) of some common flowering plant families. Among over 4,000 different plant species, more than 3,000 different types of alkaloids with diverse therapeutic properties have been identified, which exhibit anti-inflammatory, antitumor, antiviral, antibacterial, anti-asthmatic, antiarrhythmic, anti-obesity, anti-parasitic, narcotic, sedative, hypocholesterolemic, cardiovascular, hepatoprotective, and nephroprotective effects [4-11]. The consumption of many alkaloids in adequate doses is beneficial for health, while overdoses of alkaloids might be poisonous and could even cause death [4,12-19].

It is assumed that narcotine was the first plant alkaloid extracted in 1803 by Pierre Sobriquet, a French chemist, in Paris [20], followed by morphine in 1806 by Friedrich Wilhelm Adam Sertürner, a German pharmacist [21]. The term "alkaloid" (like alkali) was first used by W. Meitner in 1819 for substances that behaved like alkali [22]. It is

because the majority of plant alkaloids are weak bases, with a few exceptions, such as theobromine and theophylline (amphoteric) [23].

Although alkaloids consist of one or more carbon rings and a nitrogen atom with a variable location on the ring, their chemical structure varies greatly among alkaloids as well as plant families [24]. The majority of alkaloids are non-volatile, crystalline, bitter and colorless in their pure form, the exceptions being nicotine, pilocarpine and coniin (liquid), colchicine and berberine (yellow), and canadine (orange) [25].

CAPSAICIN

Capsaicin is responsible for the distinctive pungent taste of chili; it is a naturally occurring vanilloid alkaloid found in adequate amounts in the placental tissue and, to a lesser extent, in the seeds and fruit pericarp of chilies [26]. Capsaicin's spicy nature is due to its vanillyl moiety, which is also responsible for its detrimental consequences when used therapeutically [27]. Capsaicin is a highly volatile, hydrophobic, odorless, and colorless alkaloid with a molecular weight of 305.4 kDa and a melting point of 62–65°C. Capsaicin has a vanillyl (methyl catechol) head group and an aliphatic tail that are linked by a centralized amide bond (Fig. 1) [28].

In 1816, Christian Friedrich Bucholz [de] (1770–1818) first extracted the impurity compound from the genus Capsicum and named it "capsaicin" after the name of the genus *Capsicum*. [26]. Capsaicin was extracted almost in pure form by John Clough Thresh (1850-1932), who nomenclated it as "capsaicin" in 1876 [29-31]. However, Karl Micko extracted the pure form of capsaicin in 1898 [32,33]. Nelson in 1919 first determined the chemical composition and also partially described the chemical structure of capsaicin [33]. Ernst Spath and Stephen F. Darling chemically synthesized capsaicin for the first time in 1930 [34].

Uh Kosuge and Inagaki (Japanese pharmacists) identified and extracted similar chemical compounds in pepper and named them Capsaicinoids [35,36]. The capsaicin content of different chilies is determined using the liquid chromatography technique, which

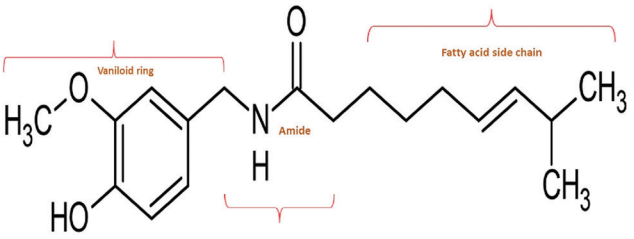

Fig. 1: Chemical structure of capsaicin

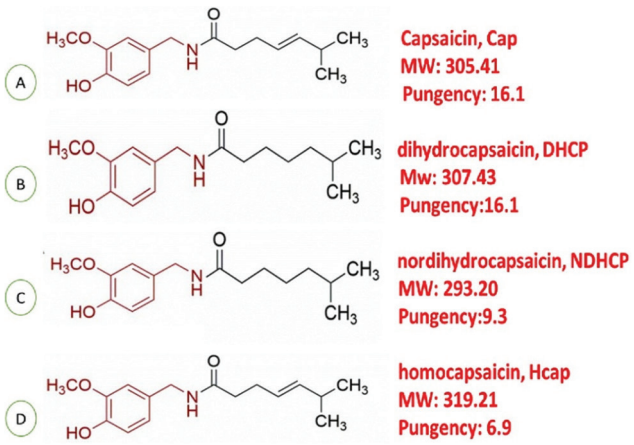

Fig. 2: Capsaicin content of different chillies by liquid chromatography technique

ranges from 0.1 to 4.25 mg/g of chili tissue (Fig. 2) [37]. *Capsicum frutescens, Capsicum annuum, and Capsicumchinese* were found to carry 0.22–20 mg of total Capsaicinoids per gram of dry weight of peppers [38,39]. The chili plant is thought to produce such compounds as defense compounds against fungi, bacteria, and herbivores [40].

The culinary and medicinal history of Capsicum dates back to 7000 BC [41]. People in hot climates have long been using *capsicum* to manage extreme heat by improving heat-dissipation regulation through capsaicin-induced skin vasodilation and perspiration [42]. Coughing, dry mouth, bronchitis, gastric ulcers, backaches, cholera, gout, hydration, rheumatism, cramping, dysentery, dyspepsia, and dentistry are all folk medical uses for *capsicum* [43,44]. Despite its widespread use, little was known about the biological action of capsaicin until recently, when its unique actions on sensory neurons were discovered [27].

Capsaicin's therapeutic effects were first discovered in the 19th century, when it was widely used by Westerners to ease itchy or scorching feelings in the extremities [45]. Buchheim (1873) and Hőgyes (1878) were among the first observers to detect the increased gastric-juice secretion in addition to the incinerated feeling generated by capsicol (partially purified capsaicin) when it came into contact with mucosal membranes, confirming the compound's early pharmacological properties [46,47]. With the advancement in capsaicin research, a transient receptor potential (cation) channel of the vanilloid receptor family, subtype 1 (TRPV1), was identified as the capsaicin receptor [48]. TRPV1 is composed of six transmembrane domains. It has a short, pore-forming hydrophobic stretch between the fifth and sixth transmembrane domains. TRPV1 is composed of six transmembrane domains. It has a short, pore-forming hydrophobic stretch between the fifth and sixth transmembrane domains. TRPV1 is activated by noxious heat (above 43 degrees Celsius), acid (pH 5.9), voltage, and a variety of lipids. Capsaicin activates TRPV1, which results in cation influx and a variety of physiological responses [49].

TRPV1 is a non-selective, ligand-gated cation channel that acts as an integrator of a variety of stimuli such as vanilloids, voltage, uncomfortable heat, endogenous lipids, protons, cations, and various inflammatory mediators. Capsaicin is a highly and prototypical exogenous activator of TRPV1. The TRPV1 discovery brought about a rebirth of faith in capsaicin's therapeutic potential [50,51]. The proposed mechanisms, which involve TRP1 activation, confirm capsaicin's analgesic effect as well as its effect on thermoregulation. Capsaicinoids' positive effects in the treatment of obesity, hypertension, diabetes, cardiovascular disease, gastro-protective, or anti-cancer activity have been evaluated and partially or entirely established based on these processes [52].

Capsaicin-containing ointments and creams have been used in medication for decades to treat prolonged chronic body pain. When applied topically, capsaicin is effective in the treatment of allergies, strep, sore muscles, osteoporosis ailments, diabetes mellitus, and other pain problems when applied topically. Topical capsaicin is sold under the trade names Menthacin, Zostrix, and Capzasin-P by a number of pharmaceutical industries [44]. Authorization of capsaicin as a medicine has extended its therapeutic value. In 2009, the European Union and the Food and Drug Administration authorized the use of an 8% capsaicin patches (Qutenza or NGX-4010) for the treatment of acute and chronic pain.

The EU authorized the use of Qutenza for pain problems such as post-herpetic neuralgia (PHN), peripheral neuropathic pain (PNP), and HIV-associated distal sensory polyneuropathy (HIV-DSP) [53,54], whereas in the United States, the FDA has only approved its usage for PHN [55]. Such investigations have clearly demonstrated capsaicin as a potent therapeutic agent. Nonetheless, the use of capsaicin in a variety of other clinical conditions has yet to be investigated [56,57].

PHARMACOLOGICAL POTENTIAL

Capsaicin has a wide range of therapeutic applications and uses in resolving a variety of human disorders due to its analgesic, anti-cancer,

anti-obesity, anti-inflammatory, and anti-oxidant characteristics (Fig. 3) [58].

Anti-inflammatory action

Several studies have shown that capsaicin, Capsaicinoids, and capsanoid compounds of chili peppers exhibit anti-inflammatory activity [59]. Studies on animal inflammation models have revealed that the anti-inflammatory effects of capsaicin were accompanied by the inhibition of inflammatory cytokines (TNF-, IL-1, and IL-6) and a transcription factor (NFκB) in a dose-dependent manner [60]. Capsaicin exerts anti-inflammatory responses in mice in lipopolysaccharide-induced inflammation and lipopolysaccharide-stimulated BV 2 microglia cells by reducing the release of inflammatory cytokines such as TNF-, IL-1, and IL-6 through inhibiting the nuclear factor-kappa B (NF-kB) and microtubule-associated protein kinase signaling pathways. (Fig. 4) [61,62].

Capsaicin and Dihydrocapsaicin (a capsaicinoid found in chili peppers) have anti-inflammatory activity by inhibiting nitric oxide (NO) production and activation of heme oxygenase1 in LPS-stimulated RAW264.7 macrophages; it also has an anti-inflammatory and preventive role in ischemia-induced retinal injuries through endogenous release of somatostatin (a growth hormone inhibitor) Capsaicin inhibits the production of LPS-induced pro-inflammatory cytokines such as IL-1, IL-6, and TNF- in a time- and dose-dependent manner by upregulating LXRs (ligand-activated transcription factors of the nuclear receptor superfamily). It indicates that LXRs have the potential to facilitate capsaicin-mediated activation of PPARs (ligand-activated transcription factors of the nuclear hormone-receptor superfamily), and persuading the suppression of NF-B (transcription factor that is essential for inflammatory responses) in the lipopolysaccharide-induced inflammatory response [64,65].

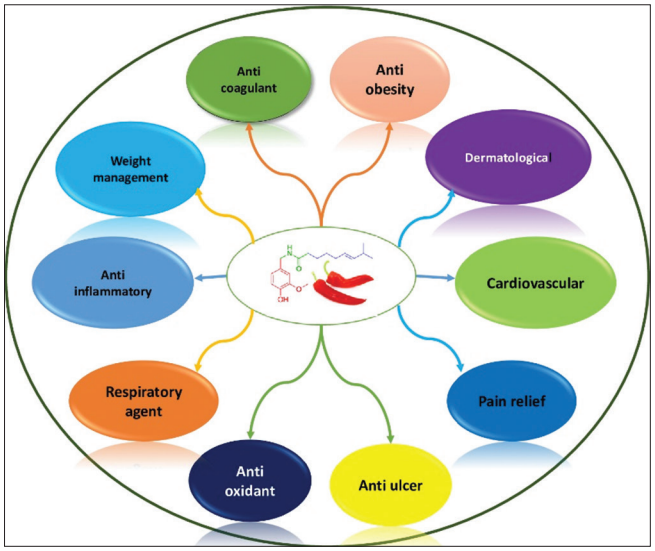

Fig. 3: Various pharmacological and physiological potential of capsaicin

Capsaicin appears to have anti-inflammatory effects on the gastritis of gerbils (Mongolian rodents) induced by Helicobacter pylori. Further, capsaicin greatly reduced neutrophils inside the antrum and corpus (stomach parts); it also reduced mononuclear cell infiltration and the presence of heterotopic proliferative glands inside the corpus. Capsaicin also inhibited TNF (tumor necrosis factor-) mRNA expression and phospho-IκB-α production in the antrum. These observations suggest that capsaicin may be useful in the prevention and treatment of Helicobacter pylori-related stomach malignancies too [66].

From the above discussion, one might conclude that capsaicin is a promising therapeutic agent that might be used to develop novel drugs for both the treatment and prevention of neuro-inflammatory disorders [62]. Even though this chemical has been used for years to treat inflammatory problems, its therapeutic relevance to preventing or treating inflammatory diseases requires further investigation [60].

Anti-cancer actions

According to the World Health Organization (WHO), cancer is a serious and substantial public health concern, and it is the second greatest cause of death worldwide [67]. The correlation between nutritional deficiencies and cancer is obvious. Eating a balanced diet and lifestyle improvement are major factors that can assist in reducing the cancer risk factor. *Aloe vera*, berries, curcuma, tea, tomatoes, citrus fruits, olive oil, and honey are examples of foods containing bioactive constituents that can influence the beginning as well as the progression of carcinogenesis through their significant impact on cell proliferation, apoptosis, and metastatic mechanisms [68-70]. Therefore, in the public and private health-care systems of the common population, taking initiatives to minimize smoking, improving diets, and enhancing physical exercise should be of higher priority [71].

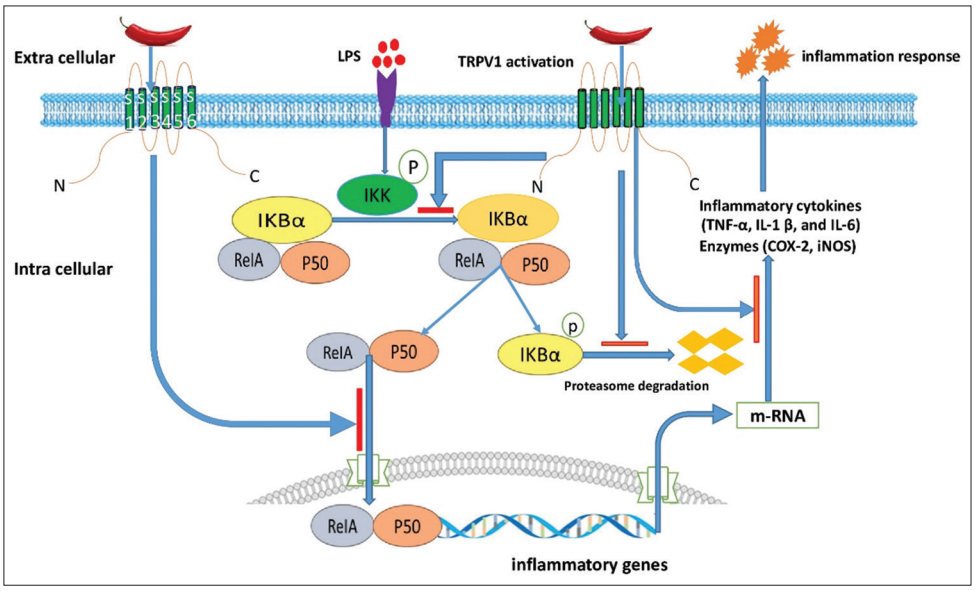

Fig. 4: Anti-neuroinflammatory responses of capsaicin

Both *in vitro* and *in vivo* studies have reported that capsaicin has a positive effect on the proliferation of cancer cells by inhibiting cell-cycle progression, autophagy, apoptosis induction, and cellular metabolic stimulation (Fig. 5), [72-76], in various cancer cell lines, including colon cancer, gastric cancer, breast cancer, cutaneous-cell carcinoma, adenocarcinoma, hepatocellular carcinoma, nasopharyngeal carcinoma, and multiple myeloma (Table 1).

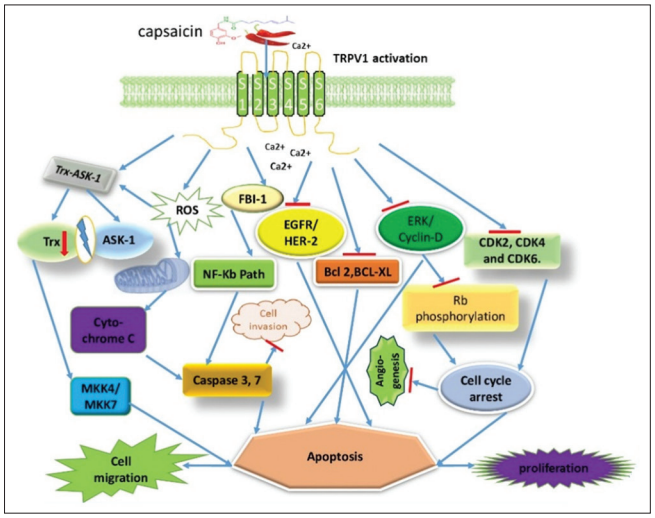

Fig. 5: Anti-cancer actions of capsaicin through employing different pathways

Capsaicin can be used to treat other types of malignancies, such as those of the pancreas, prostate gland, tongue, and lungs, and, therefore, is considered among the potential chemotherapeutic agents [77,78]. Capsaicin has been shown to trigger the death of cancerous cells in a number of clinical trials, but the exact related mechanisms are still unconfirmed. However, intracellular events, including the rise of reactive oxygen species (ROS) and Ca2+, stimulation of transcriptional regulators (NFB and STATs) and the disruption of the transition potential of the mitochondrial membrane, along with processes concerned with AMP-dependent kinase and phagocytosis, have been well established in this regard [77].

Capsaicin was found to have higher cytotoxicity against cancer cells than normal ones. It induced cell death and autophagy (a process that destroys long-lived proteins, damaged organelles, and protein aggregates) in human melanoma and the OE19 cell line, and results suggest that it might be a novel candidate-medication for melanoma treatments [79,80]. Capsaicin and DIM (3, 3'-diindolylmethane, an active compound in cruciferous vegetables) worked synergistically to inhibit cell proliferation and induce apoptosis in colorectal cancer by modulating the transcriptional activity of transcription factors NF-kB (nuclear factor kappa-B) and p53 (tumor-suppressor protein), as well as genes associated with apoptosis (genetically-programmed cell death) [81].

Table 1: Capsaicin' role in different anti-cancer mechanisms

Type of cancer	Cell lines	Role of capsaicin	References
1. Skin cancer	A375 and C8161.	• Triggered the cell apoptosis and autophagy in melanoma cells.	[80]
2. Cholangio carcinoma	HuCCT1.	• Inhibited the cell migration and invasion via the blockage of Hedgehog-pathway activation.	[94]
3. Breast Cancer	MCF-7and MDA-MB-231. MCF-7, BT-20. BT-474, SKBR-3, MDA MB231.	• Down-regulated the FBI-1-mediated NF-κB pathway, capsaicin significantly inhibited proliferation and induced apoptosis in Breast-cancer cell lines. • Inhibited cancer cell growth by inducing apoptosis and Cell cycle arrest through the mitochondrial pathway. • Inhibited cell growth and migration by inducing cell-cycle arrest and apoptosis through suppression of EGFR and HER-2 and the activation of ERK and cyclin D.	[84] [95] [96]
4. Liver cancer	SMMC-7721. LM3.	• Induced the apoptosis, generated superoxide and stimulated of both JNK and p38 MAPK pathways. • Capsaicin in combination with sorafenib achieved a markedly stronger induction of apoptosis by increasing caspase-3, Bax and poly(ADP-ribose),polymerase activity and inhibiting Bcl-2, and induction of autophagy by upregulating the levels of beclin-1 and LC3A/B II, and enhancing P62 degradation.	[86] [87]
5. Gastric cancer	AGS. SGC-7901. SW-480.	• Inhibited the invasion and migration by modulating POU3F2-mediated tNOX down-regulation. • Inhibited the cell growth by reactivating hMOF and associated H4K16ac. • Inhibited the cell growth by reactivating hMOF and associated H4K16ac.	[92] [97] [98]
6. Bladder cancer	5637. 5637, T24. TSGH8301, T24.	• Inhibited the proliferation by induction of cell-cycle arrest, and apoptosis through inhibition of CDK2, CDK4 and CDK6. • Induction of ROS production and mitochondrial membrane depolarization. • Induced the autophagy and EMT through Hedgehog signaling pathway	[99] [100] [100]
7. Prostate cancer	PC-3, LNCap, DU-145. PC-3. PC-3, LNCap, RWPE-1.	• Inhibited the cancer cell migration by down-regulation of MMP9 expression through AMPK–NF-κB signaling pathway. • Induced the apoptosis, and disruption of mitochondrial inner Tran's membrane potential by ROS generation, and activation of caspase 3, and inhibited the proliferation through the induction of ER stress and GADD153/ CHOP up-regulation. • Inhibited the cell proliferation by inducing apoptosis through inhibiting the NF-κB pathway	[101] [102] [103]

Capsaicin caused the death of prostate cancer cells in a time-and concentration-dependent manner, elevated the levels of the autophagy marker microtubule-associated protein 'light chain 3-II' (LC3-II), and facilitated the accumulation of p62 (a cargo protein). P62 is a classic autophagy receptor (a self-digesting mechanism responsible for the elimination of damaged organelles); it is a versatile protein found throughout the cell, where it participates in various signal transduction pathways and the proteasomal destruction of ubiquitinated proteins. It demonstrated that capsaicin-induced non-proliferation of prostate cancer cells contributed to the underlying capsaicin-mediated anti-carcinogenic mechanism [82]. Capsaicin increased ROS-signaling-dependent autophagy in human hepatoma by phosphorylating signal transducer and activator of transcription 3 (p-STAT3). This shows that suppressing autophagy in hepatocellular carcinoma might improve capsaicin-induced apoptosis [83].

Capsaicin reduced proliferation and induced apoptosis in breast cancer cells through down-regulating the FBI-1-mediated NF-B pathway. The findings suggested that capsaicin could be an effective way of targeting the FBI-1, which is involved in anti-proliferation and pro-apoptosis processes. FBI-1 has been characterized as a proto-oncogenic protein that represses tumor suppressor ARF gene transcription. FBI-1 expression was increased in many cancer tissues; it inhibited transcription of the Rb gene, a tumor suppressor gene involved in cell cycle arrest [83,84]. According to a National Cancer Institute study, capsaicin could have been a potential therapeutic strategy for patients with breast cancer [84].

Capsaicin could trigger the generation of ROS in the cells of HCC (hepatocellular carcinoma, a liver cancer), destroy the mitochondrial membrane potential, and stimulate the reactive oxygen scavenger "n-acetyl cysteine" (N-acetyl-cysteine, or NAC), resulting in increased apoptosis of human HCC-cells [85]. According to Bu *et al*. 2015 [86], capsaicin induced the cell-death of HCC and SMMC-7721 (a hepatocellular cancer cell line) through ROS generation and activation of the JNK (Jun N-terminal kinase) and p38 MAPK (p38 mitogen-activated protein kinase) pathways. Dai *et al*. (2018) [87] found that capsaicin and sorafenib not only increased the activity of key apoptosis-inducing proteins such as caspase 3, Bax, and poly (ADP-ribose) polymerases (PARPs), but also inhibited the anti-apoptotic protein Bcl 2 (B cell lymphoma-2) by upregulating the levels of autophagy-related genes (Be The treatment increased the induction of apoptosis by promoting the degradation of the specific autophagy protein p62; it could also prevent cancer-cell invasion and metastasis by up-regulating E-cadherin and by down-regulating N-cadherin, vimentin, MMP-2, and MMP-9.

Capsaicin suppressed bladder cancer cell development by inhibiting tNOX (tumor-associated NADH oxidase) and SIRT1 (Sirtuin1), suppressing the proliferation, pausing the migration, and delaying the cell-cycle progression in cancer cells [88]. Capsaicin also improves cell migration in bladder cancer cells by increasing cortactin and -catenin acetylation, inhibiting and promoting the inhibition of SIRT1, MMP-2, and MMP-9 [88,89]. Capsaicin inhibited the metastasis (reformation of cancer-tissue in different body-parts) of papillary thyroid-cancer cell-line (B-CPAP). By activating TRPV1 and significantly inhibiting the cancer-related proteins MMP-2 (matrix metalloproteinase-2) and MMP-9 (matrix metalloproteinase-9), it was demonstrated that targeting TRPV1 activities might be a viable strategy for the treatment of cancer [90].

Through the AMP-activated protein kinase (an energy sensor that regulates cellular metabolism), the combination therapy of docetaxel (an antineoplastic agent) and capsaicin suppressed the cancer growth in the cells of LNCap and PC3 (cultured cancer cell-lines), which suggests a clinically significant approach to the treatment of prostate cancer [91]. Capsaicin has been shown to reactivate low-expressed epigenetic regulatory enzymes in GC cells (human males absent on the first, hMOF), stimulate protein expression, and catalyze the enzyme activity regarding the acetylation of histone H4K16, thus limiting the GC cell proliferation in MGC-80 and SGC-7091 GC cell lines, and suggesting that Capsaicin has the ability to decrease the proliferation, migration and invasion of GC cells through regulation of Tumor-Associated NADH Oxidase (tNOX) involving POU Domain Transcription Factor POU3F2 [92]. Capsaicin directly engages with tNOX, resulting in its degradation through the ubiquitin-proteasome and the autophagy-lysosome systems. In the cells of p53-mutated HSC-3 (human tongue squamous carcinoma cell-line), capsaicin triggered both autophagy (body's automatic system to clean out damaged cells), and apoptosis (genetically-programmed cell death). Thus, Capsaicin could be used as a potential therapeutic strategy against oral cancer. It is hoped that this study may lead to new treatments for the disease [93].

Pain-relieving action

Capsaicin has been shown to be effective in the treatment of certain serious neuropathy problems when administered topically, intradermally, or orally [104]. When administered intravenously, subcutaneously, or topically, capsaicin significantly improved hyperalgesia and pain relief [105]. Capsaicin has been reported to have antinociceptive properties, primarily utilizing the TRPV-1-dependent pathways. Topical administration of high doses of capsaicin is often used to relieve chronic pain, TRPV1-generated repetitive excitation, and epigastric complications in people with irritable bowel syndrome; it relieves dyspepsia by desensitizing nociceptive pathways [106]. Topical capsaicin-formulations, administered in high doses, control a wide spectrum of peripheral neuropathic pain-implications by countering the progressive alterations in the nerve system [107]. Capsaicin appeared to be effective therapeutic agent to treating moderate pain in clinically or radiologically diagnosed osteoarthritis patients [108].

Capsaicin provides effective long-term pain relief and reductions in the area and intensity of pain in adult patients with chronic pain, inducing a faster onset of analgesia and exerting significantly fewer systemic adverse-effects compared to conventional therapy [109]. Besides providing significant pain relief, it has also been shown to remove tiredness and depression, improving sleep and overall quality of life [110]. Noncompliance is avoided using a single application of capsaicin. However, because of the strong burning sensation it generates, it must be used under strict supervision and after a local anesthetic injection. Since all capsaicin effects on TRPV1 are reversible, it is recommended that the application be repeated after 12 weeks [110].

The European Medicines Agency (EMA) has currently approved a high-dose of 8% capsaicin-patch for the treatment of postherpetic neuralgia (a painful condition that affects the nerve fibers and skin), associated pain, HIV-related distal sensory neuropathy, and diabetic neuropathy. The intensity of pain diminishes dramatically after 1, 2, or 3 weeks of capsaicin treatment [111]. By selectively ablation of potential vanilloid subtype 1 TRPV1+ afferent terminals, a single focused injection of capsaicin produces long-lasting analgesia for neuropathic pain. Capsaicin can be used to treat chronic pain as a stand-alone treatment or in conjunction with other drugs. Furthermore, capsaicin should be a viable treatment option for psychiatric patients suffering from persistent pain [112].

Action against obesity and weight control

Obesity is becoming more common as a result of modern lifestyles in both developed and developing countries. Obesity is a condition in which the body-fat level of a person gets increased to the point of health risk. Obesity is defined as having a body weight of 20% more than the average and serves as a portent for various health problems, particularly cardiovascular disease, diabetes mellitus, cancer, hypogonadism, and osteoarthritis [113].

Capsaicin has been shown to exert an anti-obesity effect in a variety of ways, including thermogenesis (dissipation of energy through heat production), satiety (overeating), fat oxidation, and increased energy expenditure. It can reduce energy intake, inhibit adipogenesis, decrease pancreatic and lipoprotein lipase activity, increase lipolysis in adipose

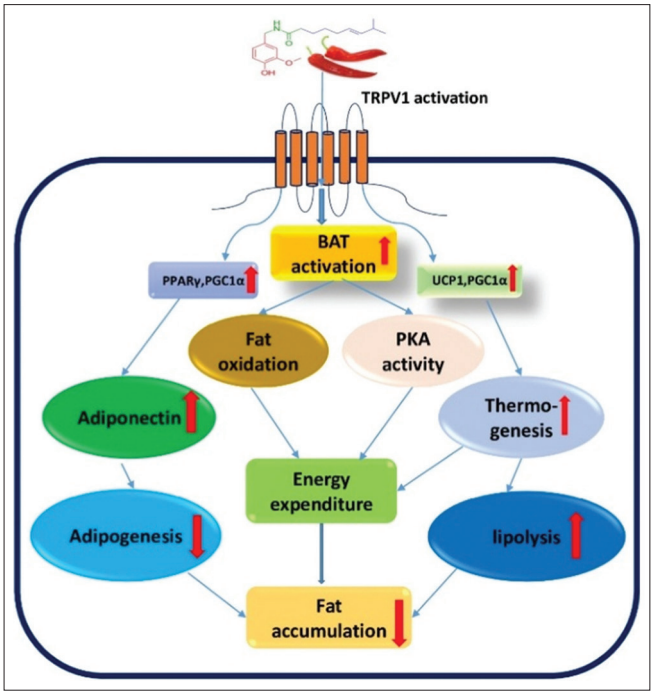

Fig. 6: General underplaying mechanism of anti-obesity activity of capsaicin through thermogenesis, lipolysis, adipogenesis, energy expenditure

tissue, inhibit adipocyte differentiation, and change adipokine release from adipose tissues. (Fig. 6) [114-122].

Capsaicin's role as an anti-obesity drug has been established in several laboratories and clinical studies. Further, intake of capsaicin-containing diets is correlated with the minimum risk of obesity in overweight or obese patients [123]. Enhanced fat-oxidation may contribute to increased energy expenditure, and an increase in oxygen consumption may be advantageous for weight loss [124]. In a double-blind, randomized and placebo-controlled study, it was observed that capsaicin reduced body weight by 0.9 kg when overweight or obese adults were treated with 6 mg/day capsinoids for 12 weeks [125]. Another randomized double-blind study showed that participants within the age-group of 30–65 years and with a BMI (body-mass index) greater than 23 kg/m^2, who were given capsinoids (10 mg/kg/day) for 4 weeks, safely lost their weight through increased VO2 max (a measure of the maximum amount of oxygen one can utilize during exercise), resting energy expenditure, and fat oxidation [126].

Brawn adipose tissues (BAT) are believed to play a significant role in cold-induced non-shivering thermoregulation in order to control the temperature of the body, which is expected to be an effective treatment for obesity-associated metabolic ailments in human beings [127]. As per Saito and Yoneshiro 2013 [128], capsaicin increased energy expenditure by activating the BAT in almost the same manner as cold temperatures do, leading to increased energy expenditure through non-shivering thermogenesis (an increase in metabolic heat production, above the basal metabolism, which is not associated with muscle activity). In an 8-week clinical experiment employing obese people, 9 mg of capsaicin elevated the BAT activity and increased thermogenesis. The findings imply that dietary capsaicin consumption may contribute to weight control by decreasing energy intake and by triggering BAT activation [129]. Adipogenesis (differentiation of pre-adipocytes into adipocytes and the fat-storing cells) is the fundamental and distinctive mechanism of the accumulation of fatty adipose tissue [130,131].

Hence, reduced adipogenesis and lipogenesis (synthesis of fatty acids and triglycerides) may potentially contribute to a reduction in obesity. Hsu and Yen 2007 [130] determined that capsaicin suppressed the expression of the proteins, namely, PPAR (peroxisome proliferator-activated receptor), C/EBP (CCAAT/enhancer binding proteins), and leptin, whilst it elevated the adiponectin protein content, thus accelerating apoptosis and inhibiting fat accumulation in the 3T3-L1 cell-line concerned with preadipocytes and adipocytes. As a result of capsaicin administration, TRPV-1 expression was reduced in adipose tissue, adiponectin expression was increased in adipose tissue, and PPAR and PGC-1 expression were enhanced in the liver [132]. Capsaicin has been shown to enhance browning in white adipocytes by activating the PPAR/3-AR signaling pathway. Thus, capsaicin may be worth considering as a treatment option for obesity (Fig. 6) [133].

Conclusively, these investigations revealed that capsaicin might help induce weight loss by reducing adipogenesis and regulating gene functions related to lipid metabolism.

Action against diabetes

Diabetes is a metabolic disorder in which the body's natural ability to regulate blood sugar levels is either inept or impaired, resulting in an inefficient or inappropriate response to the insulin hormone. Chili and its constituent, capsaicin, have been shown to have an anti-diabetic response through a number of different mechanisms, such as those inhibiting the activities of polysaccharide hydrolyzing-enzymes α-amylase and α-glucosidase [134,135], regulating body weight, and exerting hypolipidemic effects [136].

In fact, capsaicin-mediated TRPV1 stimulation led to improved insulin sensitivity in liver cells, suppression of inflammatory response, regulation of glucose homeostasis, increased insulin sensitivity in peripheral tissues, stimulation of secretion of glucagon-like peptide-1 (GLP1), improved, glucose metabolism, β-cell security from apoptosis, significant decline of fasting glucose and insulin levels, and adipocytokine-gene expression [49], resulting in the production of adipocytokine, which is involved in various processes, including inflammation, fibrosis, and thermogenesis.

Gestational diabetes mellitus (GDM) is a condition in which placental-secreted hormones make a person unable to use insulin, causing blood-sugar levels to rise rather than simply being assimilated by the cells. This may have a significant impact on the long-term health of females as well as their descendants. Ladies with GDM experience pregnancy-related health problems too, such as hypertension and obstructed labor. Capsaicin-containing supplements were found to significantly improve postprandial hyperglycemia, hyperinsulinemia, and fasting lipid metabolic alterations in women with gestational diabetes [137]. Capsaicin might reduce glucose tolerance by suppressing inflammatory responses in adipocytes (fat-storing cells) in obese patients. Consumption of capsaicin in the daily diet prevented the obesity brought about by induced sugar intolerance and by increased oxidation of fatty acids in the adipose and liver tissues, which are significant peripheral sites that influence insulin resistance [132].

Action against cardiovascular diseases

Capsaicin has a protective impact on the cardiovascular system through reducing blood pressure, mitigating coronary disease (damaged blood vessels), and preventing myocardial infarction (heart attack), which is associated with its anti-oxidative potential [138]. In studies, it has been demonstrated that dietary capsaicin reduces the risk of atherosclerosis (buildup of plaque inside arteries), hypertension, cardiac hypertrophy (abnormally large heart), and stroke (reduced blood supply to the brain) [139]. Regular consumption of chili by heart patients for four weeks is believed to enhance the resistance of plasma lipoproteins against oxidation as a result of capsaicin's antioxidant activity (Fig. 7) [140].

Capsaicin inhibits platelet aggregation through TRPV1-dependent or -independent pathways [141-143]. It travels across the platelet plasma membranes, altering membrane fluidity [131], thereby eliciting Ca2+ discharge from intracellular platelet reserves and, consequently, inducing the ADP and platelet activation triggered by thrombin (the

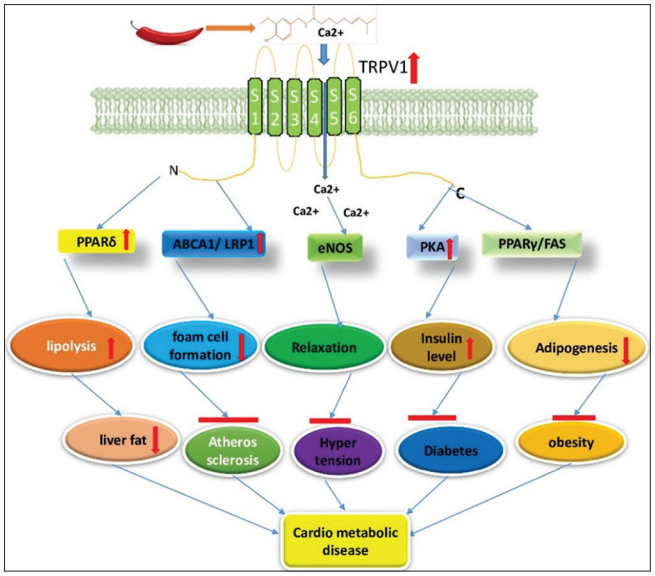

Fig. 7: Role of capsaicin in cardio metabolic disease management

coagulation factor that stops bleeding). Atherosclerosis has been associated with the initiation and progression of atherosclerosis, whereas capsaicin has been shown to delay the onset of such oxidation and/or slow its rate, leading to a rise in LDL resistance to oxidation [133]. Capsaicin decreases atherosclerosis (build-up of plaque inside arteries) through accelerating ATP-binding cassette transporter A1 (ABCA1) and diminishing the expression of LDL-related protein 1 (LRP1) in the aorta (main artery taking blood from the heart to the rest of the body) through TRPV1 stimulation (Fig. 7) [145].

The presence of capsaicin-sensitive sensory nerves in the cardiovascular system aids in the regulation of cardiovascular function by releasing CGRP (calcitonin gene-related peptide) via TRPV1 and SP (substance P, a neuropeptide) [146,147]. According to Yang *et al*. (2010) [148], dietary capsaicin had positive therapeutic effects on hyperlipidemia and atherosclerosis by reducing oxidative stress and endothelial dysfunction through activation of endothelial TRPV1 and nitric oxide (NO)-dependent pathways, which might be a unique way to prevent cardiovascular disease. Another study found that capsaicin had an effect on the endothelial nitric oxide synthase (eNOS) pathway as well as CGRP-mediated endothelium-dependent and -independent mesenteric artery relaxation [83].

Karale *et al*., 2020 [150], revealed that capsaicin played a potential role in cardio toxicity induced by doxorubicin (DOX) through suppressing serum markers and oxidative stress in heart tissues. Another study confirmed that capsaicin could minimize mitochondrial dysfunction and was able to protect cardiomyocytes (cells that generate the contractile force in the intact heart) against anoxia/re-oxygenation (A/R)-induced damage and apoptosis [150]. Capsaicin stimulated autophagy by increasing the expression of the 14-3-3 protein, decreasing inflammatory responses caused by oxidative damage, restoring mitochondrial function, and protecting cardiomyocytes from lipopolysaccharide (LPS)-induced destruction [151]. These findings indicate that capsaicin might be effective agent in the prevention of cardiovascular disorders such as atherosclerosis and coronary heart disease.

Role of capsaicin in Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the cumulative destruction of dopamine neurons in the substantia nigra pars compacta (a portion of the mid-brain) and the degradation of DA fibers inside the striatum (a brain portion involved in voluntary movements) [152]. Although the etiology of Parkinson's disease is unknown [153], information from both human-and other animal-investigations suggests that the disorder may be associated with inflammatory responses, which include microglial activation, infiltration of peripheral immune cells, specifically macrophages, and impairment of the blood-brain barrier (a network of blood vessels and tissue, made up of closely-spaced cells that helps keep harmful substances from reaching the brain) [154,155].

Both experimental as well as clinical evidence indicates that activated glia (non-neuron cells of the central nervous system) potentially produce NADPH oxidase-derived ROS and perhaps even myeloperoxidase-derived reactive nitrogen species (RNS), both of which trigger oxidative damage of DA neurons (dopaminergic neurons of the mid-brain) (Fig. 8), [156-158]. TRPV1 (a receptor protein), which is stimulated by capsaicin, appears to be widely expressed in the brain, predominantly in DA neurons, along with glial cells (microglia and astrocytes) throughout the SN (substantia nigra, a mid-brain dopaminergic nucleus having a role in motor movements).

Recent investigations have proved that TRPV1 might be a potential therapeutic approach to treat Parkinson's disease [159]. For example, TRPV1 protects DA neurons in the SN of a mouse lesioned by the ions of such drugs as MPP (1-methyl-4-phenylpridium) and MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine), or by 6-OHDA (6-hydroxydopamine, a neurotoxin) through suppressing glial-induced oxidative damage and systemic inflammation [160-162]. Nam *et al*. (2015) [163] observed that capsaicin-induced activation of astrocytic TRPV1 resulted in the production of ciliary neurotrophic factor (CNTF), which inhibited the neurodegeneration that might prove a novel therapeutic target for the treatment of Parkinson's disease. Capsaicin contributed to the reduction of pro-inflammatory mediators and prevented the degeneration of nigral dopaminergic neurons in the LPS-lesioned SN.

Further, capsaicin transitioned the pro-inflammatory M1 microglia/macrophage population to an anti-inflammatory M2 state, resulting in dopamine neuron survival. As a result, TRPV1 activation by capsaicin is anticipated to have therapeutic promise in the treatment of neurodegenerative disorders such as Parkinson's disease [164]. In MPP+-lesioned rats, delayed capsaicin treatment resulted in partial functional recovery by increasing the activity of the nigral tyrosine hydroxylase (TH) enzyme, the striatal levels of nigrostriatal dopamine (DA), and its metabolites, utilizing the ciliary neurotrophic factor (CNTF), endogenously derived from CAP-activated astrocytes via TRPV1 [165]. Abdel *et al*. explored the effects of capsaicin on epileptic seizures, neuronal damage, and oxidative damage using a rat model of status epilepticus generated by intramuscular administrations of pentylenetetrazole (PTZ) drug. They revealed that capsaicin or phenytoin reduced the neuronal damage when applied at 2 mg/kg and that capsaicin/phenytoin entirely protected the neuronal damage by lowering the MDA (malondialdehyde) and nitric oxide levels in the brain, and by decreasing the activity of GSH (reduced glutathione) and PON-1 (human-serum paraoxonase) (Fig. 8) [166]. These findings demonstrate that capsaicin might be effective for the treatment of DA abnormalities associated with Parkinson's disease.

Capsaicin and/or resveratrol (a polyphenol that acts as an antioxidant) protected mouse cerebral cortical neurons from glutamate-induced neurotoxicity; glutamate significantly reduced cell viability, whereas capsaicin and/or resveratrol administration significantly increased cell viability by decreasing glutamine-induced ROS production and apoptotic neurotoxicity [167]. Capsaicin supplementation was crucial in rescuing DA neurons, promoting striatal DA functions, and refining cognitive and behavioral recovery in treated animals by lowering the generation of pro-inflammatory cytokines as well as ROS/RNS from activated microglia-derived NADPH-oxidase.

This suggests that capsaicin and its analogues might be potential therapeutic agents for the treatment of Parkinson's disease and other neurodegenerative syndromes characterized by chronic inflammation and microglial activation-induced oxidative damage [160].

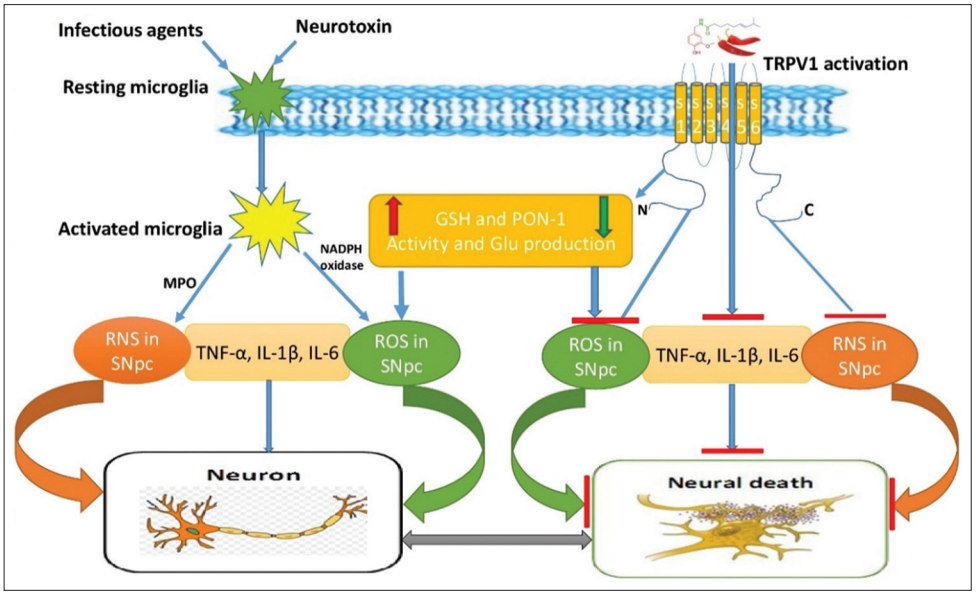

Fig. 8: (A). A possible etiology of Parkinson's disease. (B). General mechanism associated with possible role of capsaicin in Parkinson's disease management

According to Liu *et al.* [168], an imbalance between the expression of Actg1 and Gsta2 proteins might be one of the causes of cellular damage in Parkinson's disease. Capsaicin may protect damaged cells and reduce mortality by modulating the Actg1 (actin gamma 1) and Gsta2 (Glutathione S-transferase 2) proteins [168]. Thus, capsaicin may be proposed as a helpful pharmaceutical approach for treating neurodegenerative ailments, such as Parkinson's disease, in human beings.

CONCLUSION AND FUTURE PERSPECTIVES

Plants are the source of numerous pharmaceutical compounds. Human races were familiar with the use of medicinal plants and their chemical ingredients in human healthcare before their actual discovery and isolation as chemical compounds. The discoveries of plants' natural ingredients have played a pivotal role in improving human health and have become the pharmaceutical choice, despite significant competition from better and more efficient compounds produced by computational and sequential biology. Capsaicin is a naturally occurring plant alkaloid present in chili fruits in an adequate amount and is responsible for the pungency test of chili. Due to its prominent culinary and clinical applications, capsaicin has piqued the public's curiosity throughout millennia.

Despite its undesirable side effects, capsaicin is being used as a key ingredient in a wide range of formulations for the treating of numerous diseases in humans, including cancer prevention, cardiovascular and gastrointestinal system diseases, pain relief, blood sugar level maintenance, Parkinson's disease treatment, and weight loss. Capsaicin's usage as a culinary spice or medicine, on the other hand, has been restricted due to its heightened irritability, unpleasant burning sensation, and nociceptive action. This has led to the hunt for non-pungent counterparts that are free of the drug's inherent and undesired side effects, allowing for the development of more effective and bearable medications.

ACKNOWLEDGMENTS

The first author is thankful in this regard for a PhD scholarship provided by the University Grants Commission (UGC) New Delhi, India.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest regarding the publication of this manuscript.

REFERENCES

1. Veeresham C. Natural products derived from plants as a source of drugs. J Adv Pharm Technol Res 2012;3:200-1. doi: 10.4103/2231-4040.104709, PMID 23378939
2. Taylor Leslie ND. Plant Based Drugs and Medicines. Carson: Rain Tree Nutrition Inc.; 2000. p. 1-5.
3. Shu YZ. Recent natural products based drug development: A pharmaceutical industry perspective. J Nat Prod 1998;61:1053-71. doi: 10.1021/np9800102, PMID 9722499
4. Jang EJ, Kil YS, Park HR, Oh S, Kim HK, Jeong MG, *et al*. Suppression of IL-2 production and proliferation of CD4 (+) T cells by tuberostemonine. Chem Biodivers 2014;11:1954-62. doi: 10.1002/cbdv.201400074, PMID 25491339
5. Li X, Zhou R, Zheng P, Yan L, Wu Y, Xiao X, *et al*. Cardioprotective effect of matrine on isoproterenol-induced cardio toxicity in rats. J Pharm Pharmacol 2010;62:514-20. doi: 10.1211/jpp.62.04.0015, PMID 20604842
6. Xing Y, Yan F, Liu Y, Liu Y, Zhao Y. Matrine inhibits 3T3-L1 preadipocytes differentiation associated with suppression of ERK1/2 phosphorylation. Biochem Biophys Res Commun 2010;396:691-5. doi: 10.1016/j.bbrc.2010.04.163, PMID 20451501
7. Zheng J, Zheng P, Zhou X, Yan L, Zhou R, Fu XY, *et al*. Relaxant effects of matrine on aortic smooth muscles of guinea pigs. Biomed Environ Sci 2009;224:327-32. doi: 10.1016/S0895-3988(09)60063-5, PMID 19950528
8. Long Y, Lin XT, Zeng KL, Zhang L. Efficacy of intramuscular matrine in the treatment of chronic hepatitis B. Hepatobiliary Pancreat Dis Int 2004;3:69-72. PMID 14969841
9. Zhang B, Liu ZY, Li YY, Luo Y, Liu ML, Dong HY, *et al*. Anti-inflammatory effects of matrine in LPS-induced acute lung injury in mice. Eur J Pharm Sci 2011;44:573-9. doi: 10.1016/j.ejps.2011.09.020, PMID 22019524
10. Han Y, Zhang S, Wu J, Yu K, Zhang Y, Yin L, *et al*. Matrine induces apoptosis of human multiple myeloma cells via activation of the mitochondrial pathway. Leuk Lymphoma 2010;51:1337-46. doi: 10.3109/10428194.2010.488708, PMID 20528251
11. Zhang L, Wang T, Wen X, Wei Y, Peng X, Li H, *et al*. Effect of matrine on HeLa cell adhesion and migration. Eur J Pharmacol 2007;563:69-76. doi: 10.1016/j.ejphar.2007.01.073, PMID 17343841
12. Imperatore C, Aiello AD, D'Aniello F, Senese M, Menna M. Alkaloids from marine invertebrates as important leads for anticancer drugs discovery and development. Molecules 2014;19:20391-423. doi: 10.3390/molecules191220391, PMID 25490431
13. Wink M. Allelochemical properties and the râison d'être of alkaloids. Alkaloids 1993;43:1-118.
14. Wink M. Interference of alkaloids with neuroreceptors and ion channels. Stud Nat Prod Chem 2000;21:3-122. doi: 10.1016/S1572-

5995(00)80004-6
15. Wink M. Molecular modes of action of cytotoxic alkaloids: From DNA intercalation, spindle poisoning, topoisomerase inhibition to apoptosis and multiple drug resistance. Alkaloids Chem Biol 2007;64:1-47. doi: 10.1016/s1099-4831(07)64001-2, PMID 18085328
16. Wink M, Latz-Brüning B, Schmeller T. Biochemical effects of allelopathic alkaloids. In: Inderjit KM, Chester LF, editors. Principles and Practices in Plant Ecology. Boca Raton, FL: CRC Press; 1999. p. 411-22.
17. Haznedaroglu MZ, Gokce G. Comparison of anti-acetyl cholinesterase activity of bulb and leaf extracts of *Sternbergia candida* Mathew and T. Baytop. Acta Biol Hung 2014;65:396-404. doi: 10.1556/ABiol.65.2014.4.4, PMID 25475979
18. Eid SY, El-Readi MZ, Wink M. Digitonin synergistically enhances the cytotoxicity of plant secondary metabolites in cancer cells. Phytomedicine 2012;19:1307-14. doi: 10.1016/j.phymed.2012.09.002, PMID 23062361
19. Merschjohann K, Sporer F, Steverding D, Wink M. *In vitro* effect of alkaloids on bloodstream forms of *Trypanosoma brucei* and *T. congolense*. Planta Med 2001;67:623-7. doi: 10.1055/s-2001-17351, PMID 11582539
20. Dang TT, Facchini PJ. CYP82Y1 Is N-Methylcanadine 1-hydroxylase, a key noscapine biosynthetic enzyme in opium poppy. J Biol Chem 2014;289:2013-26. doi: 10.1074/jbc.M113.505099, PMID 24324259
21. Reed JW, Hudlicky T. The quest for a practical synthesis of morphine alkaloids and their derivatives by chemoenzymatic methods. Acc Chem Res 2915;48:674-87.
22. Bruneton J. Pharmacognosy, Phytochemistry, Medicinal Plants. 2nd ed. Mauritius: Intercept Ltd.; 1999. p. 1136.
23. Singla D, Sharma A, Kaur J, Panwar B, Raghava GP. BIAdb: A curated database of benzylisoquinoline alkaloids. BMC Pharmacol 2010;10:4. doi: 10.1186/1471-2210-10-4, PMID 20205728
24. Azimova S, Marat Y. Natural Compounds-alkaloids. New York: Springer Science + Business Media; 2013.
25. Kodangala C, Saha S, Kodangala P. Phytochemical studies of aerial parts of the plant *Leucas lavandulaefolia*. Pharm Chem 2010;2:434-7.
26. Bucholz CF. Chemical investigation of dry, ripe Spanish peppers. Alm Pocket Book Anal (Chem) Apoth 1816;37:1-30.
27. Rios MY, Olivo HF. Natural and synthetic alkamides. Stud Nat Prod Chem 2014;43:79-121. doi: 10.1016/B978-0-444-63430-6.00003-5
28. Zheng J, Zhou Y, Li Y, Xu DP, Li S, Li HB. Spices for prevention and treatment of cancers. Nutrients 2016;8:495-529. doi: 10.3390/nu8080495, PMID 27529277
29. Thresh JC, Thresh DP. JOHN CLOUGH THRESH, M.D., D.Sc., D.P.H. Br Med J 1932;1:1057-8.
30. King J, Felter HW, Lloyd JU. A King's American Dispensatory. Cincinnati: Eclectic Medical Publications; 1905.
31. Zur Kenntniss des Capsaïcins MK (On our knowledge of capsaicin) (in German). Z Unters Nahrungs Genussmittel. J Investig Necessit Lux 1898;1:818-29.
32. Micko K. Über den wirksamen Bestandtheil des Cayennespfeffers On the active component of cayenne pepper. Zeitschr f Untersuchung d Nahr. U Genussmittel 1899;2:411-2. doi: 10.1007/BF02529197
33. Nelson EK. The constitution of capsaicin, the pungent principle of capsicum. J Am Chem Soc 1919;41:1115-21. doi: 10.1021/ja02228a011
34. Späth E, Darling SF. Synthese des capsaicins. Chem Ber 1930;63:737-43.
35. Kosuge S, Inagaki Y, Okumura H. Studies on the pungent principles of red pepper. Part VIII. On the chemical constitutions of the pungent principles. J Agric Chem Soc 1961;35:923-7.
36. Kosuge S, Inagaki Y. Studies on the pungent principles of red pepper. Part XI. J Agric Chem Soc 1962;36:251-4. doi: 10.1271/nogeikagaku1924.36.251
37. Al Othman ZA, Ahmed YB, Habila MA, Ghafar AA. Determination of capsaicin and dihydrocapsaicin in capsicum fruit samples using high performance liquid chromatography. Molecules 2011;16:8919-29. doi: 10.3390/molecules16108919, PMID 22024959
38. Thomas BV, Schreiber AA, Weisskopf CP. Simple method for quantitation of Capsaicinoids in peppers using capillary gas chromatography. J Agric Food Chem 1998;46:2655-63. doi: 10.1021/jf970695w
39. Duelund L, Mouritsen OG. Contents of Capsaicinoids in chilies grown in Denmark. Food Chem 2017;221:913-8. doi: 10.1016/j.foodchem.2016.11.074, PMID 27979294
40. Tewksbury JJ, Manchego C, Haak DC, Levey DJ. Where did the chili get its spice? Biogeography of Capsaicinoids production in ancestral wild chili species. J Chem Ecol 2006;32:547-64. doi: 10.1007/s10886-005-9017-4, PMID 16572297
41. Meotti FC, de Andrade EL, Calixto JB. TRP modulation by natural compounds. Handb Exp Pharmacol 2014;223:1177-238. doi: 10.1007/978-3-319-05161-1_19, PMID 24961985
42. Lee TS. Physiological gustatory sweating in a warm climate. J Physiol 1954;124:528-42. doi: 10.1113/jphysiol.1954.sp005126, PMID 13175196
43. Szallasi A. Auto radiographic visualization and pharmacological characterization of vanilloid (capsaicin) receptors in several species, including man. Acta Physiol Scand Suppl 1995;629:1-68. PMID 8801775
44. Conway SJ. Trapping the switch on pain: An introduction to the chemistry and biology of capsaicin and TRPV1. Chem Soc Rev 2008;37:1530-45. doi: 10.1039/b610226n, PMID 18648679
45. Turnbull A. Tincture of capsaicin as a remedy for chilblains and toothache. Dublin Free Press 1850;1:95-6.
46. Buchheim R. Fructus capsici. J Am Pharm Assoc 1873;22:106.
47. Hőgyes A. Beitrage Zur physiologischen Wirkung der Bestandtheile des *Capsicum annuum*. Arch Exp Pathol Pharmakol 1878;9:117-30.
48. Cui M, Gosu V, Basith S, Hong S, Choi S. Polymodal transient receptor potential vanilloid type 1 nocisensor: Structure, modulators, and therapeutic applications. Adv Protein Chem Struct Biol 2016;104:81-125. doi: 10.1016/bs.apcsb.2015.11.005, PMID 27038373
49. Sun F, Xiong S, Zhu Z. Dietary capsaicin protects cardiometabolic organs from dysfunction. Nutrients 2016;8:174. doi: 10.3390/nu8050174
50. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: A heat-activated ion channel in the pain pathway. Nature 1997;389:816-24. doi: 10.1038/39807, PMID 9349813
51. Nagy I, Friston D, Valente JS, Perez JV, Andreou AP. Pharmacology of the capsaicin receptor, transient receptor potential vanilloid type-1 ion channel. Prog Drug Res 2014;68:39-76. doi: 10.1007/978-3-0348-0828-6_2, PMID 24941664
52. Werner J. Capsaicinoids-properties and mechanisms of pro-health action. In: Jeszka-Skowron M, Zgoła-Grześkowiak A, Grześkowiak T, Ramakrishna A, editors. Analytical Methods in the Determination of Bioactive Compounds and Elements in Food Food Bioactive Ingredients. Cham: Springer; 2021. doi: 10.1007/978-3-030-61879-7_8
53. Medical Review. FDA. Center for Drug Evaluation and Research; 2009. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022395s000sumr.pdf [Last accessed on 2015 Nov 27].
54. Haanpää M, Cruccu G, Nurmikko TJ, McBride WT, Axelarad AD, Bosilkov A, *et al*. Capsaicin 8% patch versus oral pregabalin in patients with peripheral neuropathic pain. Eur J Pain 2016;20:316-28. doi: 10.1002/ejp.731, PMID 26581442
55. Baranidharan G, Das S, Bhaskar A. A review of the high-concentration capsaicin patch and experience in its use in the management of neuropathic pain. Ther Adv Neurol Disord 2013;6:287-97. doi: 10.1177/1756285613496862, PMID 23997814
56. De Lille J, Ramirez E. Pharmacodynamic action of the active principles of Chillie. Chemistry 1935;29:4836.
57. Toh CC, Lee TS, Kiang AK. The pharmacological actions of capsaicin and analogues. Br J Pharmacol Chemother 1955;10:175-82. doi: 10.1111/j.1476-5381.1955.tb00079.x, PMID 14389657
58. Luo XJ, Peng J, Li YJ. Recent advances in the study on Capsaicinoids and capsinoids. Eur J Pharmacol 2011;650:1-7. doi: 10.1016/j.ejphar.2010.09.074, PMID 20946891
59. Srinivasan K. Role of spices beyond food flavoring: Nutraceuticals with multiple health effects. Food Rev Int 2005;21:167-88. doi: 10.1081/FRI-200051872
60. Srinivasan K. Anti-inflammatory influences of culinary spices and their bioactives food. Rev Int 2020;doi: 10.1080/87559129.2020.1839761
61. Li J, Wang H, Zhang L, An N, Ni W, Gao Q, *et al*. Capsaicin affects macrophage anti-inflammatory activity via the MAPK and NF-κB signaling pathways. Int J Vitam Nutr Res 2021. doi: 10.1024/0300-9831/a000721, PMID 34235954
62. Zheng Q, Sun W, Qu M. Anti-neuro-inflammatory effects of the bioactive compound capsaicin through the NF-κB signaling pathway in LPS-stimulated BV2 microglial cells. Phcog Mag 2018;14:489-94. doi: 10.4103/pm.pm_73_18
63. Kim Y, Lee J. Anti-inflammatory activity of capsaicin and dihydrocapsaicin through heme Oxygenase-1 induction in Raw264.7 macrophages. J Food Biochem 2014;38:381-7. doi: 10.1111/jfbc.12064
64. Wang J, Tian W, Wang S, Wei W, Wu D, Wang H, *et al*. Anti-

inflammatory and retinal protective effects of capsaicin on ischaemia-induced injuries through the release of endogenous somatostatin. Clin Exp Pharmacol Physiol 2017;44:803-14. doi: 10.1111/1440-1681.12769, PMID 28429852

65. Tang J, Luo K, Li Y, Chen Q, Tang D, Wang D, *et al*. Capsaicin attenuates LPS-induced inflammatory cytokine production by up regulation of LXRα. Int Immunopharmacol 2015;28:264-9. doi: 10.1016/j.intimp.2015.06.007, PMID 26093270
66. Toyoda T, Shi L, Takasu S, Cho YM, Kiriyama Y, Nishikawa A, *et al*. Anti-inflammatory effects of capsaicin and piperine on Helicobacter pylori-induced chronic gastritis in *Mongolian gerbils*. Helicobacter 2016;21:131-42. doi: 10.1111/hel.12243, PMID 26140520
67. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29. doi: 10.3322/caac.20138, PMID 22237781
68. Zanini S, Marzotto M, Giovinazzo F, Bassi C, Bellavite P. Effects of dietary components on cancer of the digestive system. Crit Rev Food Sci Nutr 2015;55:1870-85. doi: 10.1080/10408398.2012.732126, PMID 24841279
69. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochem Pharmacol 2006;71:1397-421. doi: 10.1016/j.bcp.2006.02.009, PMID 16563357
70. Garavello W, Lucenteforte E, Bosetti C, La Vecchia C. The role of foods and nutrients on oral and pharyngeal cancer risk. Minerva Stomatol 2009;58:25-34. PMID 19234434
71. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, *et al*. American cancer society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2012;62:30-67. doi: 10.3322/caac.20140, PMID 22237782
72. Oh S, Choi CH, Jung YK. Autophagy induction by capsaicin in malignant human breast cells is modulated by p38 and ERK mitogen-activated protein kinase and retards cell death by suppressing endoplasmic reticulum stress-mediated apoptosis. Mol Pharmacol 2010;78:114-25.
73. Zhang J, Nagasaki M, Tanaka Y, Morikawa S. Capsaicin inhibits growth of adult T-cell leukemia cells. Leuk Res 2003;27:275-83. doi: 10.1016/s0145-2126(02)00164-9, PMID 12537981
74. Mózsik G. Capsaicin as new orally applicable gastro protective and therapeutic drug alone or in combination with non-steroidal anti-inflammatory drugs in healthy human subjects and in patients. Prog Drug Res 2014;68:209-58. doi: 10.1007/978-3-0348-0828-6_9, PMID 24941671
75. Yang ZH, Wang XH, Wang HP, Hu LQ, Zheng XM, Li SW. Capsaicin mediates cell death in bladder cancer T24 cells through reactive oxygen species production and mitochondrial depolarization. Urology 2010;75:735-41. doi: 10.1016/j.urology.2009.03.042, PMID 19592070
76. Ito K, Nakazato T, Yamato K, Miyakawa Y, Yamada T, Hozumi N, *et al*. Induction of apoptosis in leukemic cells by homovanillic acid derivative, capsaicin, through oxidative stress-implication of phosphorylation of p53 at Ser-15 residue by reactive oxygen species. Cancer Res 2004;64:1071-8. doi: 10.1158/0008-5472.can-03-1670, PMID 14871840
77. Díaz-Laviada I, Rodríguez-Henche N. The potential antitumor effects of capsaicin. Prog Drug Res 2014;68:181-208. doi: 10.1007/978-3-0348-0828-6_8, PMID 24941670
78. Lin CH, Lu WC, Wang CW, Chan YC, Chen MK. Capsaicin induces cell cycle arrest and apoptosis inhuman kb cancer cells. BMC Complement Altern Med 2013;13:46. doi: 10.1186/1472-6882-13-46
79. Lavorgna M, Orlo E, Nugnes R, Piscitelli C, Russo C, Isidori M. Capsaicin in hot chili peppers: *In vitro* evaluation of its antiradical, anti-proliferative and apoptotic activities. Plant Foods Hum Nutr 2019;74:164-70. doi: 10.1007/s11130-019-00722-0, PMID 30835044
80. Chu H, Li M, Wang X. Capsaicin induces apoptosis and autophagy in human melanoma cells. Oncol Lett 2019;17:4827-34. doi: 10.3892/ol.2019.10206, PMID 31186689
81. Clark R, Lee J, Lee SH. Synergistic anticancer activity of capsaicin and 3, 3'-diindolylmethane in human colorectal cancer. J Agric Food Chem 2015;63:4297-304. doi: 10.1021/jf506098s, PMID 25876645
82. Ramos-Torres Á, Bort A, Morell C, Rodríguez-Henche N, Díaz-Laviada I. The pepper's natural ingredient capsaicin induces autophagy blockage in prostate cancer cells. Oncotarget 2016;7:1569-83. doi: 10.18632/oncotarget.6415, PMID 26625315
83. Chen Q, Zhu H, Zhang Y, Wang L, Zheng L. Vasodilating effect of capsaicin on rat mesenteric artery and its mechanism. Zhejiang Xue Bao Yi Xue Ban 2013;42:177-83.
84. Chen M, Xiao C, Jiang W, Yang W, Qin Q, Tan Q, *et al*. Capsaicin inhibits proliferation and induces apoptosis in breast cancer by down-regulating FBI-1-Mediated NF-κB pathway. Drug Des Dev Ther 2021;15:125-40. doi: 10.2147/DDDT.S269901, PMID 33469265
85. Chen X, Tan M, Xie Z, Feng B, Zhao Z, Yang K, *et al*. Inhibiting ROS-STAT3-dependent autophagy enhanced capsaicin-induced apoptosis in human hepatocellular carcinoma cells. Free Radic Res 2016;50:744-55. doi: 10.3109/10715762.2016.1173689, PMID 27043357
86. Bu HQ, Cai K, Shen F, Bao XD, Xu Y, Yu F, *et al*. Induction of apoptosis by capsaicin in hepatocellular cancer cell line SMMC-7721 is mediated through ROS generation and activation of JNK and p38 MAPK pathways. Neoplasma 2015;62:582-91. doi: 10.4149/neo_2015_070, PMID 25997958
87. Dai N, Ye R, He Q, Guo P, Chen H, Zhang Q. Capsaicin and sorafenib combination treatment exerts synergistic anti-hepatocellular carcinoma activity by suppressing EGFR and PI3K/Akt/mTOR signaling. Oncol Rep 2018;40:3235-48. doi: 10.3892/or.2018.6754, PMID 30272354
88. Lin MH, Lee YH, Cheng HL, Chen HY, Jhuang FH, Chueh PJ. Capsaicin inhibits multiple bladder cancer cell phenotypes by inhibiting tumor-associated NADH oxidase (tNOX) and sirtuin1 (SIRT1). Molecules 2016;21:849. doi: 10.3390/molecules21070849, PMID 27367652
89. Islam A, Yang YT, Wu WH, Chueh PJ, Lin MH. Capsaicin attenuates cell migration via SIRT1 targeting and inhibition to enhance cortactin and β-catenin acetylation in bladder cancer cells. Am J Cancer Res 2019;9:1172-82. PMID 31285950
90. Xu S, Zhang L, Cheng X, Yu H, Bao J, Lu R. Capsaicin inhibits the metastasis of human papillary thyroid carcinoma BCPAP cells through the modulation of the TRPV1 channel. Food Funct 2018;9:344-54. doi: 10.1039/c7fo01295k, PMID 29185571
91. Sánchez BG, Bort A, Mateos-Gómez PA, Rodríguez-Henche N, Díaz-Laviada I. Combination of the natural product capsaicin and docetaxel synergistically kills human prostate cancer cells through the metabolic regulator AMP-activated kinase. Cancer Cell Int 2019;19:54. doi: 10.1186/s12935-019-0769-2, PMID 30899201
92. Chen HY, Lee YH, Chen HY, Yeh CA, Chueh PJ, Lin YM. Capsaicin Inhibited Aggressive Phenotypes through down regulation of tumor-associated NADH Oxidase (tNOX) by POU Domain transcription factor POU3F2. Molecules 2016;21:733. doi: 10.3390/molecules21060733
93. Chang CF, Islam A, Liu PF, Zhan JH, Chueh PJ. Capsaicin acts through tNOX (ENOX2) to induce autophagic apoptosis in p53-mutated HSC-3 cells but autophagy in p53-functional SAS oral cancer cells. Am J Cancer Res 2020;10:3230-47. PMID 33163267
94. Lee GR, Jang SH, Kim CJ, Kim AR, Yoon DJ, Park NH, *et al*. Capsaicin suppresses the migration of cholangiocarcinoma cells by down-regulating matrix metalloproteinase-9 expression via the AMPK-NF-kappa signaling pathway. Clin Exp Metastasis 2014;31:897-907. doi: 10.1007/s10585-014-9678-x, PMID 25217963
95. Chang HC, Chen ST, Chien SY, Kuo SJ, Tsai HT, Chen DR. Capsaicin may induce breast cancer cell death through apoptosis-inducing factor involving mitochondrial dysfunction. Hum Exp Toxicol 2011;30:1657-65. doi: 10.1177/0960327110396530, PMID 21300690
96. Thoennissen NH, O'Kelly J, Lu D, Iwanski GB, La DT, Abbassi S, *et al*. Capsaicin causes cell cycle arrest and apoptosis in ER-positive and -negative breast cancer cells by modulating the EGFR/HER-2 pathway. Oncogene 2010;29:285-96. doi: 10.1038/onc.2009.335, PMID 19855437
97. Wang F, Zhao J, Liu DA, Zhao T, Lu Z, Zhu L, *et al*. Capsaicin reactivates hMOF in gastric cancer cells and induces cell growth inhibition. Cancer Biol Ther 2016;17:1117-25. doi: 10.1080/15384047.2016.1235654, PMID 27715462
98. Park SY, Kim JY, Lee SM, Jun CH, Cho SB, Park CH, *et al*. Capsaicin induces apoptosis and modulates MAPK signaling in human gastric cancer cells. Mol Med Rep 2014;9:499-502. doi: 10.3892/mmr.2013.1849, PMID 24337453
99. Chen D, Yang Z, Wang Y, Zhu G, Wang X. Capsaicin induces cycle arrest by inhibiting cyclin-dependent-kinase in bladder carcinoma cells. Int J Urol 2012;19:662-8. doi: 10.1111/j.1442-2042.2012.02981.x, PMID 22462738
100. Amantini C, Morelli MB, Nabissi M, Cardinali C, Santoni M, Gismondi A, *et al*. Capsaicin triggers autophagic cell survival which drives epithelial mesenchymal transition and chemo resistance in bladder cancer cells in a Hedgehog-dependent manner. Oncotarget

2016;7:50180-94. doi: 10.18632/oncotarget.10326, PMID 27367032
101. Mori A, Lehmann S, O'Kelly J, Kumagai T, Desmond JC, Pervan M, *et al*. Capsaicin, a component of red peppers, inhibits the growth of androgen-independent, p53 mutant prostate cancer cells. Cancer Res 2006;66:3222-9. doi: 10.1158/0008-5472.CAN-05-0087, PMID 16540674
102. Sánchez AM, Martínez-Botas J, Malagarie-Cazenave S, Olea N, Vara D, Lasunción MA, *et al*. Induction of the endoplasmic reticulum stress protein GADD153/CHOP by capsaicin in prostate PC-3 cells: A microarray study. Biochem Biophys Res Commun 2008;372:785-91. doi: 10.1016/j.bbrc.2008.05.138, PMID 18533110
103. Sánchez AM, Sánchez MG, Malagarie-Cazenave S, Olea N, Díaz-Laviada I. Induction of apoptosis in prostate tumor PC-3 cells and inhibition of xenograft prostate tumor growth by the vanilloid capsaicin. Apoptosis 2006;11:89-99. doi: 10.1007/s10495-005-3275-z, PMID 16374544
104. Attal N. Pharmacologic treatment of neuropathic pain. Acta Neurol Belg 2001;101:53-64. PMID 11379277
105. Sangeeta B, Zaman KR, Das S. A review on recent researches on Bhut Jolokia and pharmacological activity of capsaicin. J Pharm Sci Rev Res 2014;24:89-94.
106. Evangelista S. Novel therapeutics in the field of capsaicin and pain. Expert Rev Clin Pharmacol 2015;8:373-5. doi: 10.1586/17512433.2015.1044438, PMID 25959004
107. Schumacher M, Pasvankas G. Topical capsaicin formulations in the management of neuropathic pain. Prog Drug Res 2014;68:105-28. doi: 10.1007/978-3-0348-0828-6_4, PMID 24941666
108. Laslett LL, Jones G. Capsaicin for osteoarthritis pain. Prog Drug Res 2014;68:277-91. doi: 10.1007/978-3-0348-0828-6_11, PMID 24941673
109. Cruccu G, Truini A. A review of neuropathic pain: From guidelines to clinical practice. Pain Ther 2017;6:35-42. doi: 10.1007/s40122-017-0087-0, PMID 29178033
110. Derry S, Rice AS, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2017;1:CD007393. doi: 10.1002/14651858.CD007393.pub4, PMID 28085183
111. Flynn R, Plueschke K, Quinten C, Strassmann V, Duijnhoven RG, Gordillo-Marañon M et al. Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?. Clin Pharmacol Ther 2022;111:90-97.
112. Wang S, Bian C, Yang J, Arora V, Gao Y, Wei F, *et al*. Ablation of TRPV1+afferent terminals by capsaicin mediates long-lasting analgesia for trigeminal neuropathic pain. eNeuro: ENEURO 2020;7:0118. doi: 10.1523/ENEURO.0118-20.2020, PMID 32404326
113. Haslam DW, James WP. Obesity. Lancet 2005;366:1197-209. doi: 10.1016/S0140-6736(05)67483-1, PMID 16198769
114. Woo HM, Kang JH, Kawada T, Yoo H, Sung MK, Yu R. Active spice-derived components can inhibit inflammatory responses of adipose tissue in obesity by suppressing inflammatory actions of macrophages and release of monocyte chemo attractant protein-1 from adipocytes. Life Sci 2007;80:926-31. doi: 10.1016/j.lfs.2006.11.030, PMID 17196622
115. Ludy MJ, Moore GE, Mattes RD. The effects of capsaicin and capsiate on energy balance: Critical review and metaanalyses of studies in humans. Chem Senses 2012;37:103-21. doi: 10.1093/chemse/bjr100, PMID 22038945
116. Reinbach HC, Smeets A, Martinussen T, Møller P, Westerterp-Plantenga MS. Effects of capsaicin, green tea and CH-19 sweet pepper on appetite and energy intake in humans in negative and positive energy balance. Clin Nutr 2009;28:260-5. doi: 10.1016/j.clnu.2009.01.010, PMID 19345452
117. Zhang H, Matsuda H, Nakamura S, Yoshikawa M. Effects of amide constituents from pepper on adipogenesis in 3T3-L1 cells. Bioorg Med Chem Lett 2008;18:3272-7. doi: 10.1016/j.bmcl.2008.04.052, PMID 18477507
118. Baek J, Lee J, Kim K, Kim T, Kim D, Kim C, *et al*. Inhibitory effects of *Capsicum annuum* L. water extracts on lipoprotein lipase activity in 3T3-L1 cells. Nutr Res Pract 2013;7:96-102. doi: 10.4162/nrp.2013.7.2.96, PMID 23610601
119. Marrelli M, Menichini F, Conforti F. Hypolipidemic and antioxidant properties of hot pepper flower (*Capsicum annuum* L.). Plant Foods Hum Nutr 2016;71:301-6. doi: 10.1007/s11130-016-0560-7, PMID 27372805
120. Do MS, Hong SE, Ha JH, Park SM, Ahn IS, Yoon JY, *et al*. Increased lipolytic activity by high-pungency red pepper extract (var. chungyang) in rat adipocytes *in vitro*. J Food Sci Nutr 2004;9:34-8. doi: 10.3746/jfn.2004.9.1.034
121. Hwang JT, Park IJ, Shin JI, Lee YK, Lee SK, Baik HW, *et al*. Genistein, EGCG, and capsaicin inhibit adipocyte differentiation process via activating AMP-activated protein kinase. Biochem Biophys Res Commun 2005;338:694-9. doi: 10.1016/j.bbrc.2005.09.195, PMID 16236247
122. Kang JH, Kim CS, Han IS, Kawada T, Yu R. Capsaicin, a spicy component of hot peppers, modulates adipokine gene expression and protein release from obese-mouse adipose tissues and isolated adipocytes, and suppresses the inflammatory responses of adipose tissue macrophages. FEBS Lett 2007;581:4389-96. doi: 10.1016/j.febslet.2007.07.082, PMID 17719033
123. Wahlqvist ML, Wattanapenpaiboon N. Hot foods-unexpected help with energy balance. Lancet 2001;358:348-9. doi: 10.1016/S0140-6736(01)05586-6, PMID 11502310
124. Whiting S, Derbyshire E, Tiwari BK. Capsaicinoids and capsinoids. A potential role for weight management. A systematic review of the evidence Appetite. Appetite 2012;59:341-8. doi: 10.1016/j.appet.2012.05.015, PMID 22634197
125. Snitker S, Fujishima Y, Shen H, Ott S, Pi-Sunyer X, Furuhata Y, *et al*. Effects of novel capsinoids treatment on fatness and energy metabolism in humans: Possible Pharmacogenetic implications. Am J Clin Nutr 2009;89:45-50. doi: 10.3945/ajcn.2008.26561, PMID 19056576
126. Inoue N, Matsunaga Y, Satoh H, Takahashi M. Enhanced energy expenditure and fat oxidation in humans with high BMI scores by the ingestion of novel and non-pungent capsaicin analogues (capsinoids). Biosci Biotechnol Biochem 2007;71:380-9. doi: 10.1271/bbb.60341, PMID 17284861
127. Yoneshiro T, Saito M. Activation and recruitment of brown adipose tissue as anti-obesity regimens in humans. Ann Med 2015;47:133-41. doi: 10.3109/07853890.2014.911595, PMID 24901355
128. Saito M, Yoneshiro T. Capsinoids and related food ingredients activating brown fat thermogenesis and reducing body fat in humans. Curr Opin Lipidol 2013;24:71-7. doi: 10.1097/MOL.0b013e32835a4f40, PMID 23298960
129. Nirengi S, Homma T, Inoue N, Sato H, Yoneshiro T, Matsushita M, *et al*. Assessment of human brown adipose tissue density during daily ingestion of thermogenic capsinoids using near-infrared time-resolved spectroscopy. J Biomed Opt 2016;21:091305. doi: 10.1117/1.JBO.21.9.091305, PMID 27135066
130. Hsu CL, Yen GC. Effects of capsaicin on induction of apoptosis and inhibition of adipogenesis in 3T3-L1 cells. J Agric Food Chem 2007;55:1730-6. doi: 10.1021/jf062912b, PMID 17295509
131. Zhang LL, Yan Liu D, Ma LQ, Luo ZD, Cao TB, Zhong J, *et al*. Activation of transient receptor potential vanilloid type-1 channel prevents adipogenesis and obesity. Circ Res 2007;100:1063-70. doi: 10.1161/01.RES.0000262653.84850.8b, PMID 17347480
132. Kang JH, Goto T, Han IS, Kawada T, Kim YM, Yu R. Dietary capsaicin reduces obesity-induced insulin resistance and hepatic steatosis in obese mice fed a high-fat diet. Obesity (Silver Spring) 2010;18:780-7. doi: 10.1038/oby.2009.301, PMID 19798065
133. Fan L, Xu H, Yang R, Zang Y, Chen J, Qin H. Combination of capsaicin and capsiate induces browning in 3T3-L1 white adipocytes via activation of the peroxisome proliferator-activated receptor γ/β3-adrenergic receptor signaling pathways. J Agric Food Chem 2019;67:6232-40. doi: 10.1021/acs.jafc.9b02191, PMID 31075194
134. Watcharachaisoponsiri T, Sornchan P, Charoenkiatkul S, Suttisansane U. The α-glucosidase and α-amylase inhibitory activity from different chili pepper extracts. Int Food Res J 2016;23:1439-45.
135. Tundis R, Loizzo MR, Menichini F, Bonesi M, Conforti F, Statti G, *et al*. Comparative study on the chemical composition, antioxidant properties and hypoglycemic activities of two *Capsicum annuum* L. cultivars (*Acuminatum* small and *Cerasiferum*). Plant Foods Hum Nutr 2011;66:261-9. doi: 10.1007/s11130-011-0248-y, PMID 21792679
136. Earnest EO, Lawrence E, Ilevbare FR. The roles of capsicum in diabetes mellitus. Wilolud J 2013;6:22-7.
137. Yuan LJ, Qin Y, Wang L, Zeng Y, Chang H, Wang J, *et al*. Capsaicin-containing chili improved postprandial hyperglycemia, hyperinsulinemia, and fasting lipid disorders in women with gestational diabetes mellitus and lowered the incidence of large-for-gestational-age newborns. Clin Nutr 2016;35:388-93. doi: 10.1016/j.clnu.2015.02.011, PMID 25771490
138. Adaszek Ł, Gadomska D, Mazurek Ł, Łyp P, Madany J, Winiarczyk S. Properties of capsaicin and its utility in veterinary

and human medicine. Res Vet Sci 2019;123:14-9. doi: 10.1016/j.rvsc.2018.12.002, PMID 30579138

139. McCarty MF, DiNicolantonio JJ, O'Keefe JH. Capsaicin may have important potential for promoting vascular and metabolic health. Open Heart 2015;2:e000262. doi: 10.1136/openhrt-2015-000262, PMID 26113985
140. Ahuja KD, Ball MJ. Effects of daily ingestion of chilli on serum lipoprotein oxidation in adult men and women. Br J Nutr 2006;96:239-42. doi: 10.1079/bjn20061788, PMID 16923216
141. Sylvester DM, LaHann TR. Effects of Capsaicinoids on platelet aggregation. Proc West Pharmacol Soc 1989;32:95-100. PMID 2780623
142. Meddings JB, Hogaboam CM, Tran K, Reynolds JD, Wallace JL. Capsaicin effects on non-neuronal plasma membranes. Biochim Biophys Acta 1991;1070:43-50. doi: 10.1016/0005-2736(91)90144-w, PMID 1751537
143. Mittelstadt SW, Nelson RA, Daanen JF, King AJ, Kort ME, Kym PR, *et al*. Capsaicin-induced inhibition of platelet aggregation is not mediated by transient receptor potential vanilloid type 1. Blood Coagul Fibrinolysis 2012;23:94-7. doi: 10.1097/MBC.0b013e32834ddf18, PMID 22089942
144. Harper AG, Brownlow SL, Sage SO. A role for TRPV1 in agonist-evoked activation of human platelets. J Thromb Haemost 2009;7:330-8. doi: 10.1111/j.1538-7836.2008.03231.x, PMID 19036069
145. Ma L, Zhong J, Zhao Z, Luo Z, Ma S, Sun J, *et al*. Activation of TRPV1 reduces vascular lipid accumulation and attenuates atherosclerosis. Cardiovasc Res 2011;92:504-13. doi: 10.1093/cvr/cvr245, PMID 21908651
146. Zvara A, Bencsik P, Fodor G, Csont T, Hackler L, Dux M, *et al*. Capsaicin-sensitive sensory neurons regulate myocardial function and gene expression pattern of rat hearts: A DNA microarray study. FASEB J 2006;20:160-2. doi: 10.1096/fj.05-4060fje, PMID 16278290
147. Peng J, Li YJ. The vanilloid receptor TRPV1: Role in cardiovascular and gastrointestinal protection. Eur J Pharmacol 2010;627:1-7. doi: 10.1016/j.ejphar.2009.10.053, PMID 19879868
148. Yang D, Luo Z, Ma S, Wong WT, Ma L, Zhong J, *et al*. Activation of TRPV1 by dietary capsaicin improves endothelium-dependent vasorelaxation and prevents hypertension. Cell Metab 2010;12:130-41. doi: 10.1016/j.cmet.2010.05.015, PMID 20674858
149. Karale S, Yamuna PV, Jagadish V. Kamath capsaicin ameliorates doxorubicin induced cardiotoxicity in rat. Indian J Pharm Educ Res 2020;54:95-100.
150. He HH, Zhou Y, Huang J, Wu Z, Liao Z, Liu D, *et al*. Capsaicin protects cardiomyocytes against anoxia/reoxygenation injury via preventing mitochondrial dysfunction mediated by SIRT1. Oxid Med Cell Longev 2017;2017:1035702. doi: 10.1155/2017/1035702, PMID 29435095
151. Qiao Y, Wang L, Hu T, Yin D, He H, He M. Capsaicin protects cardiomyocytes against lipopolysaccharide-induced damage via 14-3-3γ-mediated autophagy augmentation. Front Pharmacol 2021;12:659015. doi: 10.3389/fphar.2021.659015, PMID 33986684
152. Beitz JM. Parkinson's disease: A review. Front Biosci (Schol Ed) 2014;6:65-74. doi: 10.2741/s415, PMID 24389262
153. Kurzawski M, Białecka M, Droździk M. Pharmacogenetic considerations in the treatment of Parkinson's disease. Neurodegener Dis Manag 2015;5:27-35. doi: 10.2217/nmt.14.38, MID 25711452
154. Mosley RL, Hutter-Saunders JA, Stone DK, Gendelman HE. Inflammation and adaptive immunity in Parkinson's disease. Cold Spring Harb Perspect Med 2012;2:a009381. doi: 10.1101/cshperspect.a009381, PMID 22315722
155. Cabezas R, Avila M, Gonzalez J, El-Bachá RS, Báez E, García-Segura LM, *et al*. Astrocytic modulation of blood-brain barrier: Perspectives on Parkinson's disease. Front Cell Neurosci 2014;8:211. doi: 10.3389/fncel.2014.00211, PMID 25136294
156. Choi DK, Pennathur S, Perier C, Tieu K, Teismann P, Wu DC, *et al*. Ablation of the inflammatory enzyme myeloperoxidase mitigates features of Parkinson's disease in mice. J Neurosci 2005;25:6594-600. doi: 10.1523/JNEUROSCI.0970-05.2005, PMID 16014720
157. Gao HM, Liu B, Zhang W, Hong JS. Critical role of microglial NADPH oxidase-derived free radicals in the in vitro MPTP model of Parkinson's disease. FASEB J 2003;17:1954-6. doi: 10.1096/fj.03-0109fje, PMID 12897068
158. Wu DC, Teismann P, Tieu K, Vila M, Jackson-Lewis V, Ischiropoulos H, *et al*. NADPH oxidase mediates oxidative stress in the 1-methyl-4-phenyl-1,2, 3, 6-tetrahydropyridine model of Parkinson's disease. Proc Natl Acad Sci U S A 2003;100:6145-50. doi: 10.1073/pnas.0937239100, PMID 12721370
159. Kong WL, Peng YY, Peng BW. Modulation of neuroinflammation: Role and therapeutic potential of TRPV1 in the neuro-immune axis. Brain Behav Immun 2017;64:354-66. doi: 10.1016/j.bbi.2017.03.007, PMID 28342781
160. Chung YC, Baek JY, Kim SR, Ko HW, Bok E, Shin WH, *et al*. Capsaicin prevents degeneration of dopamine neurons by inhibiting glial activation and oxidative stress in the MPTP model of Parkinson's disease. Exp Mol Med 2017;49:e298. doi: 10.1038/emm.2016.159, PMID 28255166
161. Park ES, Kim SR, Jin BK. Transient receptor potential vanilloid subtype 1 contributes to mesencephalic dopaminergic neuronal survival by inhibiting microglia-originated oxidative stress. Brain Res Bull 2012;89:92-6. doi: 10.1016/j.brainresbull.2012.07.001, PMID 22796104
162. Zhao Z, Wang J, Wang L, Yao X, Liu Y, Li Y, *et al*. Capsaicin protects against oxidative insults and alleviates behavioral deficits in rats with 6-OHDAinduced Parkinson's disease via activation of TRPV1. Neurochem Res 2017;42:3431-8. doi: 10.1007/s11064-017-2388-4, PMID 28861768
163. Nam JH, Park ES, Won SY, Lee YA, Kim KI, Jeong JY, *et al*. TRPV1 on astrocytes rescues nigral dopamine neurons in Parkinson's disease via CNTF. Brain 2015;138:3610-22. doi: 10.1093/brain/awv297, PMID 26490328
164. Bok E, Chung YC, Kim KS, Baik HH, Shin W, Jin BK. Modulation of M1/M2 polarization by capsaicin contributes to the survival of dopaminergic neurons in the lipopolysaccharide-lesioned substantia Nigra *in vivo*. Exp Mol Med 2018;50:1-14. doi: 10.1038/s12276-018-0111-4
165. Kim KI, Baek JY, Jeong JY, Nam JH, Park ES, Bok E, *et al*. Delayed treatment of capsaicin produces partial motor recovery by enhancing dopamine function in MPP+-lesioned rats via ciliary neurotrophic factor. Exp Neurobiol 2019;28:289-99. doi: 10.5607/en.2019.28.2.289, PMID 31138996
166. Abdel-Salam OM, Sleem AA, Sayed MA, Youness ER, Shaffie N. Capsaicin exerts anti-convulsant and neuroprotective effects in pentylenetetrazole-induced seizures. Neurochem Res 2020;45:1045-61. doi: 10.1007/s11064-020-02979-3, PMID 32036609
167. Lee JG, Yon JM, Lin C, Jung AY, Jung KY, Nam SY. Combined treatment with capsaicin and resveratrol enhances neuroprotection against glutamate-induced toxicity in mouse cerebral cortical neurons. Food Chem Toxicol 2012;50:3877-85. doi: 10.1016/j.fct.2012.08.040, PMID 22943972
168. Liu J, Liu H, Zhao Z, Wang J, Guo D, Liu Y. Regulation of Actg1 and Gsta2 is possible mechanism by which capsaicin alleviates apoptosis in cell model of 6-OHDA-induced Parkinson's disease. Biosci Rep 2020;40:BSR20191796. doi: 10.1042/BSR20191796, PMID 32537633