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CAPSAICIN: ITS BIOLOGICAL ACTIVITIES AND *IN SILICO* TARGET FISHING

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Abstract: *Capsicum annuum* L. is a rich source of capsaicin, an alkaloid, which is a very pungent compound. Due to ever growing need of capsaicin, an extensive research on its efficient cultivation as well as chemical synthesis is underway. Owing to the pungent nature of capsaicin, its analogous molecules without pungent effect are being explored. The objective of this descriptive review is to comprehensively present the updates on the bioactivities of capsaicin. Additionally, the *in silico* target fishing approach has been used to identify the possible protein targets of capsaicin. This article will definitely provide future perspectives of research on capsaicin.

Keywords: capsinoids; capsaicin; pharmacology

Capsicum annuum L. or chilli, an extensively found vegetable belonging to the family Solanaceae (1, 2), has earned a great nutritional value (3, 4) since chilli pepper is a promising source of vitamins and minerals (5, 6). Chilli pepper also contains many biological active compounds, including capsaicinoids, which are pungent in nature (7). Famous compounds that are enlisted as capsaicinoids are capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin and homocapsaicin. Major part (greater 90%) of chili pepper capsaicinoids consists of two most potent compounds, capsaicin and dihydrocapsaicin. The only difference between the structures of these compounds is the saturation of the acyl group (8).

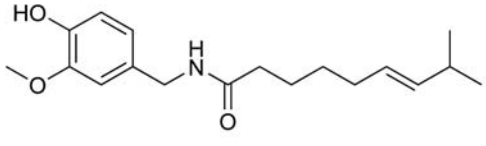

Figure 1. The chemical structure of capsaicin

Due to pharmaceutical and dietary importance, an extensive research on its efficient cultivation as well as chemical synthesis is in progress (9-13). Various bioactivities of the capsaicinoids, and capsaicin in particular, are found to be antioxidant (14), anti-inflammatory (15), anticancer (16), and many others (17). Owing to the pungent nature of capsaicin, its analogous molecules without pungent effect are being explored (18, 19).

The molecular weight, chemical name and molecular formula of this phenol, capsaicin, are 305.40 g/mol, trans-8-methyl-N-vanillyl-6-nonenamide and $C_{18}H_{27}NO_3$, respectively. Capsaicin, chemically, is a decylenic acid amide of vanillyl amine. The chemical structure of this lipophilic alkaloid is given in Figure 1 (20). Out of two isomeric forms (cis/trans) of capsaicin, it always exists as the trans-isomer due to the presence of steric hindrance in the cis-form (21).

As far as pharmacokinetics is concerned, besides excellent oral absorption of capsaicin, the studies have demonstrated its efficient absorption across skin as well (22). The half-life and the time to reach maximum plasma capsaicin concentration

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after oral intake are 24 h and 1 h, respectively (23, 24) The compounds produced by hepatic metabolism of capsaicin include 16-hydroxycapsaicin, 17-hydroxycapsaicin and 16,17-dihydrocapsaicin (25, 26)

Drug development process has been modernized through *in silico* target fishing, a high-throughput computational method. This approach helps in efficient and effective investigation of the mode of action of small drug molecules by identifying their protein targets (27, 28) Nowadays, *in silico* drug target identification can be conducted through many methods including Chemical Similarity Search approach (29).

The objective of this descriptive review is to comprehensively present the updates on the bioactivities of capsaicin. Additionally, the *in silico* target fishing approach was used to identify possible protein targets of capsaicin.

Biological activities of capsaicin

Antioxidant activity

The antioxidant activity of capsaicin has been reported by few investigators (30, 31). Reference to the chemical structure of capsaicin, the presence of methoxy group on ortho-position to hydroxyl group has been considered to be responsible for the antioxidant activity of capsaicin (30). One of the studies conducted to assess the antioxidant activity of pure capsaicin and capsicum extracts (also called the oleoresins) has revealed that capsaicin contents influence the antioxidant activity of capsicum extracts (32). Capsaicin has also been observed to efficiently prevent lipid peroxidation, protein oxidation, enzyme activity loss and antioxidant activity loss-induced by γ radiation. It reveals the role of capsaicin against oxidation and radiations (33). Another study has revealed the antioxidant role of capsaicin reporting that peroxyl radicals derived from 2,2'-azobis(2,4-dimethylvaleronitrile) are also scavenged by capsaicin (34). These results elaborate the dietary importance of this natural antioxidant for health.

Antimicrobial activity

Due to the emergence of resistance against existing antimicrobial agents, there is growing interest in exploring antimicrobial properties of plants and plant-origin active natural compounds (35-37). The bactericidal action of capsaicin against Gram-positive and Gram-negative bacteria has been reported by few researchers (38). For example, capsaicin and its analogues have been found to be bactericidal against *Bacillus subtilis* (39, 40), *Streptococcus mutans* (41), *Streptococcus pyogenes* (42), *Helicobater pylori* (43, 44), *Escherichia coli* (45), and *Colletotrichum capsici* (46). This bactericidal action of capsaicin was attributed to its capability to damage the bacteria cell membrane (47). Moreover, capsaicin has been found to be non-cytotoxic, since no effect of capsaicin was noted on cell viability at low concentration (48-52). For example, capsaicin at sublethal concentrations suppresses the production of cholera toxin in *Vibrio cholerae* and of α-toxin in *Staphylococcus aureus* (49, 51); capsaicin inhibits *Staphylococcus aureus* intracellular invasion (50) and suppresses the biofilm synthesis by *Porphyromonas gingivalis* (48, 52). Another study has reported that capsaicin has the highest antimicrobial potential, based on the MIC value, against Gram positive bacteria (including *Enterococcus faecalis*, *Bacillus subtillis*, and *Staphylococcus aureus*), Gram negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*) and yeast (*Candida albicans*) as compared to that of two other compounds of *Capsicum annuum,* dihydrocapsaicin and chrysoeriol (53). Capsaicin has also been formulated as different dosage forms to enhance its effectiveness. For example, gelatin, acacia and tannins microparticles loaded with capsaicin have also been tested and found to be microbiologically effective against *Botrytis cinerea* and *Aspergillus niger* for the prolonged time in comparison to capsaicin. In addition, tannins microparticles loaded with capsaicin showed the synergetic increase in microbiological effectiveness (54). The antimicrobial feature of capsaicin microemulsion against *Staphylococcus aureus*, *Salmonela enterica* and *Escherichia coli* has also been compared with that of crude capsaicin. It was evident from results that the crude capsaicin was more effective against these three bacteria than that of capsaicin microemulsion (55). As a future perspective, the antimicrobial effect of capsaicin *in vivo* is needed to be determined since there is no antimicrobial study, to date, of capsaicin *in vivo*.

Antifungal activity

The mammalian cells are susceptible to various fungal infections. For example *Penicillium expansum* is involved in the production of patulin (56-58). Patulin is a mycotoxin, which produces genotoxicity of mammalian cell and the post-harvest decay in apples (59, 60). Due to the public concern and the emergence of resistant strains against the most widely used chemical fungicides (61, 62), new approaches for the biological control of fungus are being investigated (63). In this context, the experimental studies have proved the capsaicin as a new alternative antifungal agent against different fungal

species. For example, *Penicillium expansum* has effectively been treated by using capsaicin with a minimum inhibitory concentration of 122.16 µg/mL (64). Capsaicin has also been formulated as different dosage forms to enhance its effectiveness. For example, cellulose-capsaicin graft showed better antifungal activity in comparison to capsaicin alone against *Trametes versicolor* and *Gloeophyllum trabeum*. These results elaborate the promising antifungal potential of capsaicin.

Antiviral activity

Although capsaicin does not exhibit direct antiviral activity, it has been reported that cutaneous HSV disease in guinea pigs can be treated with capsaicin (65, 66). Moreover, since herpes simplex virus (HSV) infections can be treated by disrupting the normal virus-neuron interactions, it can be achieved by using the neuropharmacologic compounds, such as capsaicin. The cis isomer of capsaicin, civamide, has been reported to be useful for the topical management of primary or recurrent experimental genital herpes (67). Civamide, with antinociceptive activity (68), is a useful intranasal therapy for the relief of migraine (69).

Neuronal and analgesic activity

Many studies have described the selective neurophysiological and neurochemical actions of capsaicinon sensory neurons with unmyelinated C-fiber processes. It comprises of primary afferents of spinal ganglia (70), which play a role in spreading virus and persisting the HSV infection (71). Additionally, capsaicin exerts a skin burning effect, which is reduced after multiple applications of capsaicin to skin. This repeated application of capsaicin leads to the desensitization of skin neurons. This phenomenon could be the basis of the pain relief properties of capsaicin. Thus, in spite of unpleasant pungency of capsaicin, it is largely employed in skin diseases, including postherpetic neuralgia, a condition linked with chronic nerve pain owing to the damage produced by the varicella zoster virus (72).

Vascular and metabolic activity

Transient receptor potential vanilloid 1 (TRPV1) receptors belong to an important group of receptors, which are present in many tissues, especially on nociceptive sensory neurons (73). These receptors play an important role in metabolism (74). Capsaicin has been introduced as an activator of TRPV1 receptors (75). The activation of TRPV1 receptors not only induce the calcium influx (76-78), but also leads to the augmented expression of important proteins including endothelial nitric oxide synthase (eNOS), uncoupling protein 2 (UCP2), Krüppel-like factor 2 (KLF2), peroxisome proliferator-activated receptor δ (PPAR-δ), peroxisome proliferator-activated receptor γ (PPAR-γ), COX-2 and liver X receptor α (LXRα) (78-87). These changes, alternatively, affect the vascular and metabolic activities. For example, endothelium-dependent vasodilation in rodents has been noted by administering capsaicin-rich diet (88, 89). In addition, the increased cholesterol export from foam cells and resultantly, the plaque formation is hindered by highly expressed LXRα under the effect of capsaicin (90). In gastrointestinal tract, metabolic rate is raised under the influence of capsaicin-mediated activation of TRPV1 (91, 92). Additionally, highly expressed UCP2 acts as an antioxidant and is helpful in the protection of liver in non-alcoholic fatty liver disease (93-96). In short, dietary capsaicin has shown its antiatherosclerotic, antidiabetic, antiobesity, and antihypertensive agent in rodent studies (97). Moreover, after treating with topical patches loaded with capsaicin, an increase in exercise time to ischemic threshold in cardiac patients has been reported (98). Future studies should be focused on the capsaicin-loaded drug delivery systems to promote the vascular and metabolic health.

Anticancer activity

Current pharmaceutical research is mainly focused on the discovery of natural bioactive compounds, in particular present in our diet, against cancer (98). Since chilli pepper is a general component of our daily food, the intake of capsaicin is very common (99). Numerous studies were conducted to explore the anticancer effect of the pure capsaicin and pepper plant extracts (100-102). The anticancer action of pure capsaicin was found to be lower than that of pepper plant extracts; it could be due to the synergistic effect of diverse active moieties (e.g., other capsaicinoids) present in the extract (103-105). Two types of associations have been noted between cancer and capsaicin. Firstly, a variety of results on the genotoxicity and carcinogenicity of capsaicin *in vitro* and *in vivo* have been reported (106, 107). The authors attributed this activity to the carcinogenic effect of capsaicin metabolites on DNA (108). However, no scientific base has been provided to explain these findings since there is a question mark on the purity of capsaicin, i.e., capsaicin-containing foods are contaminated with known carcinogens (109). Secondly, there are many studies that support the anticancer effects of the pure capsaicin in different types of cancers such as

prostate (110-113), colorectal (114, 115), lung (116-124), gastric (125-128), and pancreatic cancer (129-146). These studies have narrated different modes of action of capsaicin, such as the induction of apoptosis (147) as well as the suppression of cytochrome P450 enzymes, and inducible COX-2 mRNA expression (148). The obstruction of the translocation of nuclear factor κB (NF-κB) (149), activator protein 1 (AP-1) (150), and signal transducer and activator of transcription (STAT3) signaling pathway (151) are the other modes of anticancer activity of capsaicin. Thus, the use of dietary capsaicin in the chemoprevention of cancer is advantageous for health (Table 1).

Potential target of capsaicin

In spite of wide use of capsaicin, its underlying modes of action are unclear (152). After summarizing above narrated literature, we predicted the potential targets of capsaicin using PASS (Prediction of Activity Spectra for Substances), a software, on the basis of its structure. The SMILE of capsaicin was added as an input data to PASS, while the output data showed large number of possible activities of capsaicin with a probability of Pa > 0.7 (probability to be active) (Table 2). In order to further narrow down the search, protein-protein interaction network was constructed using STITCH, a database of protein interactions. This database integrates various sources of information, i.e., text mining, experimental evidences, and other data bases such as STRING. To construct the protein interaction network, we selected targets with a confidence score greater than 0.4. The obtained predicted targets of capsaicin and their probabilistic confidence score are given in Table 3. The protein network of capsaicin is presented in Figure 2. In the confidence view of this Figure, stronger interactions are symbolized by thicker lines.

Table 1. Applications of capsaicin for human health.

Benefits	Mode of action	References
Antioxidant	Prevention of lipid peroxidation, protein oxidation, enzyme activity loss, and antioxidant activity loss-induced by gamma radiation	32, 33
Antibacterial	Bactericidal against	46, 50
Antifungal	Genotoxicity	59-63
Antiviral	Growth suppression	65, 68
Neuronal and analgesic	Neurophysiological and neurochemical actions	70
Vascular and metabolic	The activation of TRPV1 receptors not only induce the calcium influx	76-89
Anticancer	Induction of apoptosis as well as the suppression of cytochrome P450 enzymes and inducible COX-2 mRNA expression. The obstruction of the translocation of nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), and signal transducer and activator of transcription (STAT3) signaling pathway	109-124

Table 2. Predicted capsaicin targets.

Abbreviations	Protein targets	Score
TRPA1	Transient receptor potential cation channel, subfamily A, member 1	0.724
TRPV1	Transient receptor potential cation channel, subfamily V, member 1	0.724
TRPM8	Transient receptor potential cation channel, subfamily M, member 8	0.679
ADHFE1	Alcohol dehydrogenase	0.651
PRKACA	Protein kinase, cAMP-dependent, catalytic, α	0.567
CTNS	Cystinosis, nephropathic	0.528
QX-314	QX-314 (263.4 g/mol)	0.519
zingerone	Zingerone (194.2 g/mol)	0.519
piperine	Piperine (285.3 g/mol)	0.519
PRKCE	Protein kinase C, ε	0.501

Table 3. List of activities with a probability at Pa > 0.7 (probability to be active).

Pa	Activity
0.928	Vanilloid 1 agonist
0.840	Vanilloid agonist
0.813	Mucomembranous protector
0.796	Linoleatediol synthase inhibitor
0.799	Ubiquinol-cytochrome-c reductase inhibitor
0.771	TP53 expression enhancer
0.701	Antinociceptive
0.726	Antieczematic

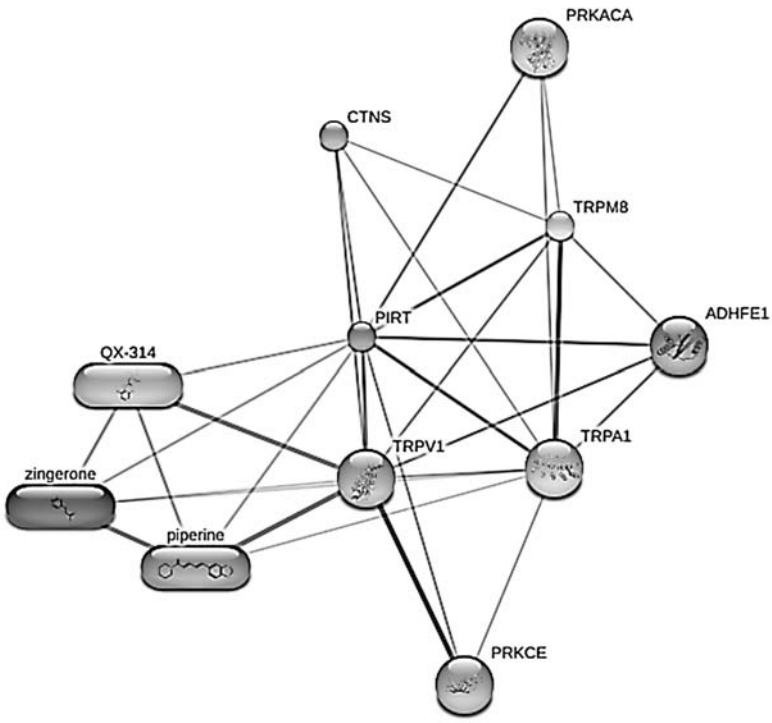

Figure 2. The protein network of capsaicin. The proteins and their associations are shown by the nodes and edges.

Toxicity of capsaicin

Capsaicin is an extremely irritant substance that produces dermal, eye, oral, and inhalational toxicity (153, 154). The dermal LD_{50} of capsaicin is > 512 mg/kg in mouse. It may produce burning, conjunctivitis in eyes, abdominal pain, and bronchoconstriction on exposure to skin, eyes, gastrointestinal tract and lungs, respectively (155, 156).

CONCLUSION

Capsaicin is an important bioactive compound having antioxidant, antibacterial, antifungal, antiviral, neuronal and analgesic, vascular and metabolic, and anticancer activities. Capsaicin is an interesting pharmaceutical compound that should be evaluated, in the future, for other bioactivities including antihyperglycemic and neuroprotective studies for promising health effects. Moreover, pharmacokinetic evaluation (i.e., absorption, distribution, metabolism and excretion) of capsaicin should also be conducted to interpret the association of plasma capsaicin concentration level with its therapeutic effect. There is no study on the toxicity of capsaicin in spite of its long term use as dietary element. *In silico* target fishing has indicated eight potential targets of

capsaicin. Further *in silico* and experimental validation is needed to confirm these results leading to the opening of new horizons of drug development. In this context, the initial docking studies will be conducted in the future to examine the binding mode of capsaicin with these enzymes to reveal the possible orientation and strength of binding affinity between capsaicin and the recently identified target proteins. Following docking, MD simulation will be conducted to expand the insight into the structural dynamics and stability of capsaicin in complex with these proteins.

Conflict of interest

The authors declare no conflicts of interest.

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