The Pharma Innovation Journal 2023; 12(2): 250-255

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; 12(2): 250-255

www.thepharmajournal.com
Received: 01-11-2022
Accepted: 05-12-2022

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Capsicum: A potential source of capsaicinoids with broad-spectrum ethno pharmacological applications

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DOI: https://doi.org/10.22271/tpi.2023.v12.i2d.18427

Abstract
Chili peppers are the major source of nature capsaicinoids, which consist of capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin and homocapsaicin, etc. Capsaicinoids are found to exert multiple pharmacological and physiological effects including the activities of analgesia, anticancer, anti-inflammation, antioxidant and anti-obesity. Therefore, capsaicinoids may have the potential value in clinic for pain relief, cancer prevention. In addition, capsaicinoids also display the benefits on cardiovascular and gastrointestinal system. The present article reviews the scientific literature on above aspects with particular emphasis on identifying the key regional issues which need to be addressed urgently by the policy makers in order to harness its potential as an important source of capsaicinoids. Further, an attempt has been made to collate the potential of capsaicinoids in various ethno pharmacological applications such as, body temperature regulation, anti-obesity treatments and as antioxidant and antimicrobial agent. We anticipate that this literature analysis of traditional medicinal uses and experimental trials of capsicum using modern scientific approaches shall provide a basis for suggesting important areas where sincere research efforts are warranted to bridge the gap between traditional medicinal knowledge and modern biomedical knowledge.

Keywords: Potential source, capsaicinoids, broad-spectrum ethnopharmacological

Introduction
Chilli plant (*Capsicum annum* L. Family: Solanaceae) is used as a spice in the preparation of food. The discovery and development of bioactive compounds from the chilli fruits, based on their traditional uses, play an important role in developing the scientific evidence of their potential pharmaceutical, cosmetic and food applications (Diniz do Nascimento *et al.*, 2020) [18]. The nutritional composition of chilli fruits are presented in table-1. The main chemical constituent of chilli fruits is capsaicin, a homovanillic acid derivative (8-methyl-N-vanillyl-6-nonenamide) is an active component of the genus *Capsicum* (Murakami *et al.*, 2001) [41]. It also contains various polyphenols, amino acids which have various pharmaceutical and nutritional importance.

Antioxidant activity
Hot peppers are a good source of antioxidants because of presence of flavonoids, phenolic acid, ascorbic acid, capsaicinoids etc. Capsaicin and dihydrocapsaicin was found to inhibit iron-mediated lipid peroxidation and copper-dependent oxidation of low-density lipoprotein (Murakami *et al.*, 2001) [41]. Capsaicin prevent the oxidation of oleic acid at cooking temperatures (Henderson and Slickman. 1999) [27] and also formation of lipid hydroperoxides from the autoxidation of linoleic acid (Henderson and Henderson. 1992) [26]. All capsinoids and their analogues showed, at noncytotoxic concentrations for vanillyl nonanoate, a noteworthy efficacy as chain-breaking antioxidants in scavenging lipid peroxyl radicals and effect due to their capacity to donate hydrogen atoms and delocalize the resulting radical sites (Rosa *et al.*, 2002) [49]. Capsiate showed protective effect on the reduction of the levels of total lipids, total unsaturated fatty acids and cholesterol and the cellular antioxidant vitamin E, inhibiting the increase of MDA, conjugated dienes fatty acids hydroperoxides and 7-ketocholesterol in the plasma and kidney (Rosa *et al.*, 2005) [50]. Capsaicin was found to be more effective the melatonin in suppressing the formation of lipid hydroperoxides but not as effective as BHT (Henderson *et al.*, 1999) [28].

Table 1: Nutritional composition of chilli fruits with recommended dietary allowances (RDA)

Principle	Nutrient Value	Percent of RDA
Energy	40 Kcal	2
Carbohydrates	8.81 g	7
Protein	1.87 g	3
Total fat	0.44 g	2
Dietary fiber	1.5 g	3
Vitamins		
Folates	23 µg	6
Niacin	1.244 mg	8
Pantothenic acid	0.201 mg	4
Pyridoxine	0.506 mg	39
Riboflavin	0.086 mg	6.5
Thiamin	0.72 mg	6
Vitamin A	952 IU	32
Vitamin C	143.7 mg	240
Vitamin E	0.69 mg	4.5
Vitamin K	14 µg	11.5
Minerals		
Calcium	14 mg	1.5
Copper	0.129 mg	14
Iron	1.03 mg	13
Magnesium	23 mg	6
Manganese	0.187 mg	8
Phosphorous	43 mg	6
Selenium	0.5 µg	1
Zinc	0.23 mg	2

Source: USDA National Nutrient data base.
*Nutritional valve per 100g of chilli fruits.

Anti-inflammatory activity
Traditionally, capsaicin has used to treat inflammatory diseases such as allergic rhinitis, neuralgia after shingles, refractory female urethral syndrome, spontaneous recalcitrant anal pruritus, and solid tumors. Capsaicin reduces the secretion of inflammatory cytokines interleukins, tumor necrosis factor (TNF-α) and nitric acid (NO) by inhibiting the nuclear factor-kappa B and microtubule-associated protein kinase signaling pathways and thereby reduced lipopolysaccharide-induced inflammatory response in macrophages (Li *et al.*, 2021) [39]. Capsaicin and nordihydrocapsiate inhibits early and late events in T cell activation, including CD69, CD25 and ICAM-1 cell surface expression, progression to the S phase of the cell cycle and proliferation in response to TCR and CD28 co-engagement (Sancho *et al.*, 2022) [51]. Capsaicin and dihydrocapsaicin inhibits nitric oxide (NO) production and inducible NO synthase protein and mRNA expression in LPS-stimulated RAW264.7 macrophages (Kim and Lee, 2014) [34]. The pungent capsaicin and non-ivamide as well as the tingling t-pellitorine exhibits anti-inflammatory potential by inhibition of ERK1/2 phosphorylation. Capsaicin derivatives containing nitroindole in the tail region and a nitro group on the 4-hydroxybenzyl residue at the head region exhibited the highest activity for inhibition of tumor necrosis factor-alpha TNF-alpha production (Chancharunee *et al.*, 2018) [11].

Antiobesity activity
Obesity comes from the storage of surplus energy in fat cells through the abnormal metabolism of energy in the body and is considered as a major cause of several metabolic diseases (Bray 2000) [7]. Methanol extract from hot pepper (*Capsicum annuum*) significantly reduce the manifestation of LPL mRNA up to 50.9% (Baek *et al*., 2013) [4]. Capsaicin ingestion was found to be reduce the energy intake during positive energy balance and suppresses the hunger and induce satiety more during negative than during positive energy balance (Reinbach *et al*., 2009) [48]. Tropical application of 0.075% capsaicin to male mice fed on a high-fat diet significantly decreases the weight gain, decreases lipid accumulation in the mesenteric and epididymal adipose tissues (Lee *et al*., 2013) [36]. Capsaicin in food (approximately 0.002g) increases energy expenditure and also reduce energy and fat intake (Janssens *et al*., 2014) [32]. Capsaicin inhibits the proliferation and differentiation of preadiocytes and accumulation of intracellular triglyceride and decreases he expression of lipoprotein lipase, liptin and PPAR-γ type (Feng *et al*., 2014) [21] 70:30 aqueous: ethanol extraction of 5 mg/ml of sweet pepper has 66% α-amylase inhibitory activity (Watcharachaisoponsiri *et al.*, 2016) [60]. 0.1,1,5 and 10 micromole of capsaicin decreases the lipid accumulation during adipocyte differentiation of bovine bone marrow mesenchymal stem cells for 2,4 and 6 days (Jeong *et al*., 2014) [33].

Hypertension
Hypertension is a disease in which the pressure on the walls of blood vessels increases. Red hot peppers intake will reduces the blood pressure because of its active principle capsaicin (trans-8-methyl-N-nanillyl-6-nonenamide) derived from homovanillic acid (Chapa-Oliver and Mejía-Teniente 2016) [12]. In some studies, capsaicin administration increases the systolic blood pressure (SBP), body temperature and heart rate (Varga *et al.*, 2005; Caterina *et al.*, 1997) [58, 9]. In animals pretreatment with 5 mg capsaicin reduces the mean systolic blood pressure (Virus *et al*., 1981) [59]. In rats SBP starts decreases at capsaicin treatment at 15 mg/kg at the 4th month stage (Yang *et al*., 2010) [61]. In some studies supplementation with a paprika xanthophyll capsule (0.9 mg) for 12 weeks reduces the SBP and DBP in adults (Amini *et al*., 2021) [3].

Anticancer activity
Anticancer properties of capsaicin is mainly by modifying the functions of many genes involved in cancer cell life span, growth arrest, angiogenesis and metastasis (Hanahan and Weinberg, 2011, Clark and Lee, 2016) [25, 14]. Capsaicin's is found to inhibit cell proliferation and induce increased cell cycle arrest and apoptosis (Chapa-Oliver and Mejía-Teniente, 2016) [12]. It induces apoptosis in more than 40 distinct cancer lines cells like pancreas, colon, prostate, liver, esophagus, bladder, skin, leukemia, lung and endothelial cells (Bley *et al.*, 2012) [6]. In cell cycle, cyclin-dependent kinases (CDKs) and CDK inhibitors are essential for cell cycle (Aggarwal and Shishodia, 2006) [2]. It is reported that capsaicin inhibits CDK_2, CDK_4 and CDK_6 inhibiting the proliferation of 5637 bladder carcinoma cells via cycle arrest (Chen *et al.*, 2012) [13]. Capsaicin is found to induce *p*53 phosphorylation, where *p*53 is a tumor suppressor which prevents cell proliferation by inducing cycle arrest and apoptosis in in response to cell stress such as damage to DNA, hypoxia and activation of oncogenes (Ito *et al.*, 2004) [31]. Angiogenesis is an important process in cancer cell growth and tumor metastasis (Park *et al.*, 2014) [44], however cytokines and vascular endothelial growth factor (VGEF) regulates angiogenesis. Treatment of endothelial cells with capsaicin blocked the sprouting and development of VEGF-induced vessels in p38 mitogen activated protein kinases (MAPK), protein kinase B (PKB),

and focal adhesion kinase (FAK) activation (Bhutani *et al.*, 2007; Chakraborty *et al.*, 2014) [5, 10].

Antifungal activity

Carotenoid mixture containing capsanthin and capsorubin effects the growth of *Aspergillus flavus* and inhibits its aflatoxins productions at low temperature (Santos *et al.*, 2010) [52]. Peptides isolated from chilli pepper seed contains lipid transfer protein (LTP) which inhibits the growth of the fungus *Fusarium oxysporum*, *Colletotrichum lindemuthianum* (Cruz *et al.*, 2010) [15]. *In-vitro* extracts of capsaicin extracted from *Capsicium spp.* Fruits have inhibitory effect on growth of *Pencicillium expansum* upto 14 days which is a causal agent of apple blue mould (Fieira *et al.*, 2013) [21]. n-hexane extracts of dried seeds of *Capsicum frutescence* show inhibition against *Candida albicans* where inhibition zone of 14.4 mm while ethyl extractformed largest inhibition zone of 15.0 mm against *Candida krusei* (Gurnani *et al.*, 2016) [23]. Ethyl acetate extract of Capsicum chinense inhibits the mycelial growth at 100 µL and 200 µL against three fungi *Sclerotinia sclerotiorum*, *Rhizopus stolonifer* and *Colletotrichum gloeosporioides* (Santos *et al*., 2022) [53]. Ethanolic extracts of Capsicum chinense fruits have inhibitory effects on growth of Aspergillus papasiticus and its aflatoxins production at 150 µL/mL (Buitimea-Cantúa *et al*., 2020) [8]. Carbopol-based formulation which release 50% of capsaicin within 52 h have good antifungal activity against *Candida albicans* (Goci *et al.*, 2021) [22].

Antibacterial activity

Iron oxide ($Fe_{880}O$) nanoparticles (IONPs) were synthesised via a chemical reaction by mixing hot red pepper with waste rust iron extract at 300 °C for 1.5 hours resulting antibacterial activity in both gram positive and gram negative bacterial (Abid and Kadhim 2021) [1]. The acetonitrile extract of *Capsicum chinense* in different concentrations, was effective on both the gram positive and gram negative bacteria *Escherichia coli* and *Staphylococcus aureus*. (Das *et al.*, 2018) [17]. Aqueous and methanol extracts of *Capsicum annuum*, *Capsicum frutescens*, and *Capsicum chinense* fruits has antibacterial activity against eight human pathogenic bacterial strains namely *Bacillus subtilis*, *Staphylococcus aureus*, Micrococcus luteus, *Escherichia coli*, *Pseudomonas aeruginosa*, *Shigella dysenteriae*, *Shigella flexneri* and *Vibrio cholera* (Sen *et al*., 2016) [55]. *In vitro* antimicrobial activity of *C. frutescens* seed extracts inhibition against *Pesudomaonas aeruginosa*, *Klebsilla pneumonae*, *Staphylococcus aureus* and *Candida albicans* (inhibition zone ≥ 13 mm) (Gurnani *et al.*, 2016) [24]. Ethanol extracts of oleoresin from two *Capsicum annuum* L. types namely curly red and big red chilli shows antibacterial activity against pathogenic bacteria (Gram-positive bacteria: *Staphylococcus aureus, Staphylococcus epidermis* and Gram-negative bacteria: *Escherichia coli, Pseudomonas aeruginosa*). The inhibition zone of curly red chilli oleoresin for *S. aureus*, *S. epidermis*, *E coli* and *P. aeruginosa* were 18.25, 17, 24 and 2.9 mm, respectively, while that of big red chilli oleoresin for the same bacteria were 2.86, 2.02, 1.06 and 1.65 mm, respectively (Nurjanah *et al.*, 2014) [42].

Alzheimer's disease

Alzheimer disease is induced by the increasing amount of one kind of decisive peptide called as amyloid-beta (Aβ) deposited within the cytosol in the nervous components, which is mainly due to increased amount of amyloid precursor protein (APP) by its respective enzyme, β-secretase. According to Perumal and Chong (2022) [45] Ethanolic extract of *Capsicum frutescens* (EECF) in the concentrations of 1mg/ml and 2 mg/ml has inhibition against acetylcholinesterase (AChE) and *β*-Secretase (BACE-1). Methanolic extracts of pepper fruits (*Capsicum annum*) inhibited beta secretase and AChE activities. Similarly, the phenolic extracts inhibited amyloid aggregation and also destabilized preformed amyloid fibrils (Ogunruku, 2014) [43]. Oxidative stress is a major contributor in the progression of Alzheimer disease. Capsaicin prevents the redox cycling cycling of iron and induces the lipid peroxidation, thus, capsaicin has important implications in the prevention or treatment of neurodegenerative diseases such as Alzheimer disease (Dairam *et al*., 2008) [16].

Gastrointestinal benefits

Capsaicin enhance the fat digestion and absorption in high-fat fed animals through the stimulation of liver to produce and secrete bile rich in bile acids (Platel *et al*., 2002) [46]. Administration of capsaicin (15 mg) for 8 weeks increased the activities of pancreatic digestive enzymes such as lipase, amylase, trypsin and chymotrypsin as well as the activities of small intestinal digestive enzymes such as alkaline acid phosphatase, disaccharidases (Platel and Srinivasan., 2000) [47]. Capsaicin decreases the chemo-sensitivity of oesophageal mucosa to gastric acid in patients with gastroesophageal reflux disease (GERD) (Herrera-Lopez *et al*., 2010) [29]. Ingestion of chilli (200-360 mg) daily for four weeks prevented the incidence of gastric ulceration in rats (Teng *et al*., 1998) [57] by inhibiting gastric acid secretion and increase of gastric mucosal blood flow that is., gastric hyperaemia (Satyanarayana., 2006) [54]. Capsaicin plays important role in gastrointestinal secretion. Low doses of capsaicin inhibits the basal acid output and enhances HCO^{-}_{3} secretion in the stomach of rats and in the duodenum of healthy human as well as in patients with different gastrointestinal diseases (Mózsik., 2014) [40]. Ingestion of chilli have protective role against *H. pylori* which is associated with gastroduodenal disease because of capsaicin content (Zeyrek and Oguz., 2005) [62] and also it inhibits growth of other food borne gastrointestinal pathogens such as *Listeria monocytogenes*, *Salmonella typhimurium* and *Bacillus cereus* (Dorantes *et al.*, 2008) [19].

Regulating body temperature

The capsaicin receptor is activated both by capsaicin and heat, indicating a possible role in thermoregulation (Lee, 1954) [39]. Capsaicin has been known to decrease body temperature (hypothermia) in multiple species, including humans (Szallasi and Blumberg., 1999) [56]. Capsaicin administration 5 mg/kg simulates the systems regulating heat loss and heat production simultaneously and independently, such that they have no reciprocal inhibition (Kobayash *et al*., 1998) [35]. The capsaicin-induced heat production and heat loss are controlled separately by the brainstem and by the forebrain, respectively, and the body temperature regulation is performed without an integrative centre (Lee *et al.*, 2000) [38]. In an experiment, six young healthy men who ate Tabasco hot sauce with dinner had an elevated body temperature during the first sleep cycle, making it harder for them to fall asleep and to sleep well

(Hori., 1984) [30].

Conclusion

Chilli and its active constituents especially capsaicin, phenolic components showed various pharmaceutical importance. While the scientific literature on the role of capsaicinoids as an antioxidant molecule and antimicrobial (antifungal and antibacterial) agent clearly supports the traditional application of chilli in treating various ailments. However, systematic and more extensive ethno medicinal investigations are yet to be carried out to provide new insights into the other traditional uses of this important plant. The impact of capsaicinoids on body temperature regulation has been established experimentally. Further research efforts should be directed towards understanding the underlying mechanisms. Capsaicin has been shown also to have potential application in anti-obesity treatments. Various experiments on the effect of capsaicinoids on obesity have provided differential response and hence, more comprehensive studies are required to understand the exact mechanisms behind it. It also has many gastrointestinal benefits due to capsaicin at low concentration. The chemo preventive and chemotherapeutic effects of capsaicin have also been reported. Nevertheless, the researchers are still divided in their opinion regarding the role of capsaicin in carcinogenic processes, which also requires further exploration. Chilli has been shown potential application in hypertension, Alzheimer's disease and anti-inflammatory activity. Although capsaicin is used as part of the human diet without causing any known adverse health effects, the recent toxicological studies have revealed a large number of physiological and pharmacological effects on the biological system and hence a safe exposure level of capsaicin for human consumption needs to be established.

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