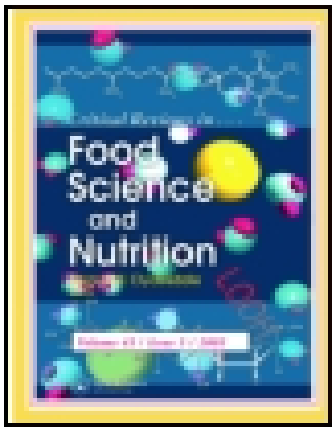

Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Biological Activities of Red Pepper (Capsicum annuum) and Its Pungent Principle Capsaicin: A Review

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Accepted author version posted online: 12 Feb 2015.

To cite this article: Krishnapura Srinivasan (2015): Biological Activities of Red Pepper (Capsicum annuum) and Its Pungent Principle Capsaicin: A Review, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2013.772090

To link to this article: http://dx.doi.org/10.1080/10408398.2013.772090

Biological activities of red pepper (*Capsicum annuum*) and its pungent principle capsaicin: A review

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Abstract

Capsaicin, the pungent alkaloid of red pepper (*Capsicum annuum*) has been extensively studied for its biological effects which are of pharmacological relevance. These include: cardio protective influence, anti-lithogenic effect, anti-inflammatory and analgesia, thermogenic influence, and beneficial effects on gastrointestinal system. Therefore, capsaicinoids may have the potential clinical value for pain relief, cancer prevention and weight loss. It has been shown that capsaicinoids are potential agonists of capsaicin receptor (TRPV1). They could exert the effects not only through the receptor-dependent pathway but also through the receptor-independent one. The involvement of neuropeptide Substance P, serotonin, and somatostatin in the pharmacological actions of capsaicin has been extensively investigated. Topical application of capsaicin is proved to alleviate pain in arthritis, post-operative neuralgia, diabetic neuropathy, psoriasis, etc. Toxicological studies on capsaicin administered by different routes are documented. Capsaicin inhibits acid secretion, stimulates alkali and mucus secretion and particularly gastric mucosal blood flow which helps in prevention and healing of gastric ulcers. Antioxidant and anti-inflammatory properties of capsaicin are established in a number of studies.

Chemopreventive potential of capsaicin is evidenced in cell line studies. The health beneficial hypocholesterolemic influence of capsaicin besides being cardio protective has other implications, viz., prevention of cholesterol gallstones and protection of the structural integrity of erythrocytes under conditions of hypercholesterolemia. Beneficial influences of capsaicin on gastrointestinal system include digestive stimulant action and modulation of intestinal ultra structure so as to enhance permeability to micronutrients.

Key words: Red pepper, Capsaicin, Pain relief, Anti-inflammatory, Cardio protective, Cancer preventive, Thermogenic, Vanilloid receptor

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INTRODUCTION

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the active component of chili peppers, belonging to the genus Capsicum. Chili peppers are extensively used in food as pungent spice, particularly in tropical countries. This capsaicinoid responsible for the pungency of the spice is also an irritant that produces a sensation of burning in any tissue with which it comes into contact. Capsaicin and several related compounds are called capsaicinoids and are produced as a secondary metabolite by chili peppers, probably as deterrents against certain herbivores and fungi. Pure capsaicin is a hydrophobic, colorless, odorless, crystalline compound. Capsaicin is the main capsaicinoid in chili peppers, followed by dihydrocapsaicin. These two compounds provide about twice hotness to the taste and nerves as the minor capsaicinoids. Hotness is measured in Scoville units which indicate the number of times the substance has to be diluted in order that the pungency is not perceived. Scoville heat units of capsaicin and dihydrocapsaicin are 16×10^6 and 15×10^6, respectively. [**Fig.1 here**]

Capsaicin is present in large quantities in the placental tissue (which holds the seeds), the internal membranes and, to a lesser extent, the other fleshy parts of the fruits of Capsicum plants. The seeds themselves do not produce any capsaicin, although the highest concentration of capsaicin can be found in the white pith of the inner wall, where the seeds are attached (Govindarajan, 1986). Capsaicin is believed to be synthesized in the interlocular septum of chili peppers by addition of a branched-chain fatty acid to vanillylamine; specifically, capsaicin is made from vanillylamine and 8-methyl-6-nonenoyl Coenzyme-A (Fujiwake et al., 1980).

HYPOCHOLESTEROLEMIC AND HYPOLIPIDEMIC EFFECTS OF CAPSAICIN

Red pepper, known for its characteristic pungency and its pungent principle capsaicin have been reviewed for their biological activity (Surh and Lee, 1995; Majid et al., 1997). Lee (1963) was probably the first investigator who studied the metabolic changes caused by feeding red pepper. The beneficial influence of red pepper or its pungent principle capsaicin on lipid metabolism as documented by several investigators is listed in **Table-1**. While studying the influence of red pepper and capsaicin on fat absorption in rats on a choline-free high hydrogenated fat (40%) diet, Sambaiah et al. (1978) observed that 5% red pepper or equivalent levels of capsaicin (15 mg%) included in the diet had a tendency to lower serum and liver cholesterol levels. In another investigation, Srinivasan et al. (1980) has reported a reduction in serum total cholesterol levels in rats on a 10% groundnut oil diet incorporated with 1.5, 3.0, or 15 mg% capsaicin. In yet another study, capsaicin at as low as 0.2 mg% in the diet led to a lowering of serum total cholesterol in both 10 and 30% fat-fed rats (Srinivasan and Satyanarayana, 1987). An increase in LDL-cholesterol and a reduction in HDL-cholesterol were also observed in the 30% hydrogenated fat group. In a subchronic toxicity study (Monsereenusorn, 1983), rats were administered 50 mg/kg body weight/day of capsaicin by gavage or 0.5 g/kg /day of a crude extract of capsicum fruit for 60 days. At 30, 40, 50 and 60 days, plasma total cholesterol levels were significantly reduced along with triglycerides and phospholipids.

The effect of 14 mg% capsaicin in a diet containing 30% lard has been studied (Kawada et al., 1986). The dose of capsaicin fed to rats was reported to be related to that commonly ingested by the Thai people. At the end of the 10 day isocaloric feeding period, serum cholesterol and pre-β-lipoprotein levels were not altered. The influence of capsaicin has also been studied in sucrose-induced hypertriglyceridemia in rats (Srinivasan and Satyanarayana, 1988). Capsaicin was fed at 0.15, 1.5, and 15 mg% levels in the diet (the lowest dose is comparable to human intake) for a period of one week. Total cholesterol and HDL-cholesterol were either significantly elevated.

The efficacy of capsaicin as a hypocholesterolemic agent has also been investigated in animals fed cholesterol in their diets. Sambaiah and Satyanarayana (1980) have reported that the serum cholesterol levels in rats on a 1% cholesterol + 5% red pepper diet were lower than those not fed with red pepper. Liver cholesterol was lower in the red pepper as well as capsaicin (an equivalent level of 15 mg%) fed groups. Fecal excretion of free cholesterol and of bile acids was enhanced in animals fed the spice and capsaicin. The anti-hypercholesterolemic efficacy of dietary capsaicin has been evidenced in rats fed an atherogenic high-cholesterol diet, and such an influence also resulted in countering of the changes in membrane lipid profile in the erythrocytes (Kempaiah and Srinivasan, 2002). In streptozotocin-induced diabetic situation however, dietary capsaicin did not show any beneficial hypolipidemic property (Babu and Srinivasan, 1997).

Intubation of rabbits with 8 mg capsaicin/ rabbit (body wt of about 850 g/day for 35 days did not have any effect with regard to plasma cholesterol, triglyceride and HDL-cholesterol when they were on a normal diet (Negulesco et al., 1983). In contrast, in rabbits on a 0.5% cholesterol

diet, capsaicin had a beneficial effect in that the plasma cholesterol, triglycerides and total cholesterol:HDL-cholesterol ratio were significantly lower than in animals fed cholesterol only. Turkeys on a 2-3 mg capsaicin/kg feed for 9 days along with 0.5% cholesterol had lower total serum cholesterol than the controls (Ki et al., 1982). Hypercholesterolemia was produced by feeding a 0.2% cholesterol-supplemented diet and capsaicin and dihydrocapsaicin were administered daily via the buccal route at dose of 4 mg per bird for 6 weeks (Negulesco et al., 1987). In animals on a normal diet, total cholesterol, LDL-cholesterol and HDL-cholesterol concentrations in plasma were increased whereas VLDL-cholesterol was significantly decreased. Plasma total and LDL-cholesterol were significantly lower in birds on the cholesterol diet administered dihydrocapsaicin. Both the compounds brought about a reduction in VLDL-cholesterol and an increase in HDL-cholesterol in the cholesterol fed group. Dihydrocapsaicin was more effective than capsaicin. The effect of capsicum oleoresin on dietary hypercholesterolemia was observed in gerbils at a dose of 75 mg/kg body weight/day (Gupta et al., 2002). The oleoresin reduced serum cholesterol and triglycerides as well as liver cholesterol and triglycerides. Capsaicin oleoresin feeding prevented the accumulation of cholesterol and triglycerides in the liver and aorta. The fecal excretion of cholesterol and triglycerides were significantly increased in oleoresin fed gerbils.

The possible mechanism of action of capsaicinoids is the net effect of decreased cholesterol absorption and increased excretion of cholesterol and bile acids in the feces which may lead to a decrease in plasma LDL-cholesterol concentration by induced expression of hepatic LDL receptors (Negulesco et al., 1987). These authors also have discussed the differences in response

between normal and cholesterol-fed animals to possible hypocholesterolemic compounds. It has been demonstrated that dietary capsaicin stimulates hepatic conversion of cholesterol to bile acids through a stimulation of the activity of cholesterol-7α-hydroxylase, an important pathway for elimination of cholesterol from the body (Srinivasan and Sambaiah, 1991). However, simultaneous stimulation of cholesterol synthesis as well through the activity of HMG-CoA reductase by this spice principle suggests that there may not be any significant contribution of the stimulation of bile acid biosynthesis to the hypocholesterolemic action of this spice principle, and the latter action may solely be due to interference with exogenous cholesterol absorption.

A recent study on hamsters has investigated the effect of capsaicinoids on plasma lipids, functionality of aorta including atherosclerotic plaque development, cholesterol absorption biomarker, fecal sterol excretion, and gene expression of major receptors, enzymes, and transporters involved in cholesterol metabolism (Liang et al., 2012). Capsaicinoids were beneficial in reducing plasma total cholesterol, improving lipoprotein profile and decreasing aortic plaque in high-cholesterol fed situation. Dietary capsaicinoids increased the fecal excretion of total acidic sterols possibly mediated by up-regulation of cholesterol-7Ŭ-hydroxylase and down-regulation of liver X receptor alpha. Plasma sterol analysis demonstrated that capsaicinoids decreased the ratio of plasma campesterol/cholesterol, suggesting they decreased cholesterol absorption.

Heat processing of red pepper results in a significant loss of its active principle capsaicin (Srinivasan et al., 1992; Suresh et al., 2007). The hypocholesterolemic potency of raw and

pressure-cooked red pepper were evaluated in experimental rats rendered hypercholesterolemic by feeding cholesterol-enriched diet and maintained for 8 weeks on 5% red pepper containing diet (Manjunatha and Srinivasan, 2008). The results suggested that although heat processing of red pepper by pressure-cooking resulted in a considerable loss of the active principle capsaicin, the hypolipidemic potency of the parent spice was not significantly compromised.

INFLUENCE OF CAPSAICIN ON BILIARY CHOLESTEROL AND BILE ACIDS; ANTI-LITHOGENIC INFLUENCE

Feeding of 7.5 and 15 mg% capsaicin to rats led to a significant increase in biliary total bile acids (Bhat et al., 1984). One of the implications of hypocholesterolemic influence is antilithogenic potential. Since capsaicin besides being hypocholesterolemic agent, also enhances bile secretion and influence its composition, its influence on gallstone formation has been examined. Dietary capsaicin (0.015%) caused a significant reduction in the formation of gallstones in mice and hamsters maintained on a lithogenic diet (Hussain and Chandrasekhara, 1992; 1993). Further, capsaicin effected a marked regression of pre-established gallstones in mice (Hussain and Chndrasekhara, 1994a). Increased cholesterol saturation index, cholesterol: Phospholipid ratio and cholesterol: bile acid ratio in the bile caused by lithogenic diet was countered by dietary capsaicin. The anti-lithogenic influence of this spice compound was attributable to the cholesterol-lowering effect of these in blood and liver, and their ability to lower cholesterol saturation index by altering the bile composition. When a combination of capsaicin and curcumin were given during experimental induction of cholesterol gallstone (CGS)

in mice, there was no additive influence in reducing the incidence of CGS, nevertheless the combination was more beneficial in reducing the oxidative stress in lithogenic situation (Shubha et al., 2011). The antilithogenecity of capsaicin has been considered to be due not merely to their ability to lower cholesterol saturation index but also to their influence on biliary proteins (Hussain and Chndrasekhara, 1994b).

PROTECTIVE EFFECT ON ERYTHROCYTE INTEGRITY

Hyperlipidemic conditions are believed to affect the fluidity of red blood cells (Cazana et al., 1990). Hypolipidemic spice compound capsaicin in the diet might offer beneficial protective influence on the integrity of erythrocyte membranes, which are presumably altered in hyperlipidemic situation. In rats rendered hypercholesterolemic by feeding a cholesterol-enriched diet for 8 weeks, erythrocyte membranes were relatively enriched in cholesterol, resulting in elevated cholesterol: phospholipid ratio of their membranes affecting their structural integrity (Kempaiah and Srinivasan, 2002). Inclusion of capsaicin (0.015%) along with high-cholesterol in the diet produced not only the hypolipidemic effect, but also countered this altered lipid profile of erythrocyte membranes and thus corrected the increased osmotic fragility of erythrocytes (Kempaiah and Srinivasan, 2002). Dietary capsaicin partially countered the changes in erythrocytes of hypercholesterolemic rats, *viz*., fatty acid profile of the membranes, phospholipid composition of the membrane bilayer, and reduced Ca^{2+},Mg^{2+}-ATPase (Kempaiah and Srinivasan, 2005). ESR spectra and fluorescence anisotropy parameters also revealed altered fluidity of erythrocytes in hypercholesterolemic rats which was significantly reversed by dietary capsaicin. In rats rendered hypertriglyceridemic by maintaining them on a high (30%) fat diet for

8 weeks, the lipid profile of erythrocyte membranes was not affected, but the erythrocytes displayed a resistance to osmotic lysis (Kempaiah & Srinivasan 2006). Inclusion of capsaicin (0.015%) along with high-fat in the diet which produced the hypotriglyceridemic effect appeared to beneficially correct this altered osmotic fragility of erythrocytes.

ANTIOXIDANT EFFECTS OF CAPSAICIN

Lipid peroxidation in human erythrocyte membranes was found to be inhibited by capsaicin (Salimath *et al*., 1986). The antioxidant property of capsaicin in terms of inhibiting lipid peroxidation in rat liver (Reddy and Lokesh, 1992) and in soybean phosphatidylcholine liposomal biomembrane has been reported (Okada and Okajima, 2001). Capsaicin is observed to inhibit copper ion-induced lipid peroxidation of human LDL (Naidu and Thippeswamy, 2002). The data suggested that capsaicin is an effective antioxidant and offer protection against oxidation of human LDL. Capsaicin inhibited the lipid peroxidation in rat liver mitochondria induced by ADP/Fe^{2+} significantly, more than the well-known antioxidant α-tocopherol (Kogure et al., 2002). Capsaicin was also found to scavenge 1,1'-diphenyl-2-picrylhydrazyl (DPPH) radicals in membranes. Capsaicin was found to scavenge radicals both at/near the membrane surface and in the interior of the membrane. Vanillin and 8-methyl-6-noneamide were major reaction products of capsaicin with DPPH radicals, thus suggesting that the radical scavenging site of capsaicin is the C7-benzyl carbon. Phenolic compounds of various spices, including capsaicin modulate 5-lipoxygenase (5-LO) in human PMNL cells, the key enzyme involved in the biosynthesis of leukotrienes (Prasad et al., 2004).

Wistar rats administered capsaicin (*i.p.* 3 mg/kg body weight) for 3 consecutive days showed a reduction of oxidative stress measured as malondialdehyde in the liver, lung, kidney and muscle (Lee et al., 2003). From this study, it is hypothesized that capsaicin can be a potent antioxidant even when consumed for a short period. The influence of capsaicin on the antioxidant status of red blood cells and liver tissue in hyperlipidemic rats is reported (Kempaiah and Srinivasan, 2004a). Capsaicin (0.015%) in the diet which produced the hypotriglyceridemic effect was also effective in reducing the oxidant stress, which was indicated by countering of the depleted antioxidant molecules and antioxidant enzymes in erythrocytes and liver, and decreasing of the elevated lipid peroxide content. The beneficial influence of capsaicin on the antioxidant status of red blood cells and liver in induced hypercholesterolemic rats is also evidenced (Kempaiah and Srinivasan, 2004b). The depletion in intracellular thiols and GSH in red blood cells under hypercholesterolemic situation was effectively countered by dietary (0.015%) capsaicin. Glutathione reductase activity that was lowered in hypercholesterolemic conditions was completely countered by the dietary spice principle. Decreased hepatic total thiols in the hypercholesterolemic situation were partially corrected by dietary capsaicin treatment. Similarly, the lowered activities of hepatic antioxidant enzymes - GSH-reductase, GSH-transferase, catalase, and superoxide dismutase in hypercholesterolemic rats were effectively countered by the dietary capsaicin.

ANTI-INFLAMMATORY PROPERTY OF CAPSAICIN

With increasing interest in alternatives to non-steroidal anti-inflammatory agents in the management of chronic inflammation, the use of food based approaches is emerging. Lipid peroxides play a crucial role in arthritis and other inflammatory diseases. Capsaicin is considered to exhibit an anti-inflammatory property based on several studies. Both *in vitro* and *in vivo* animal studies have documented the anti-inflammatory potential of capsaicin (of red pepper). Animal studies have revealed that capsaicin also lowers the incidence and severity of paw inflammation and also delay the onset of adjuvant induced paw edema in rats (Reddy and Lokesh, 1994d; Joe and Lokesh, 1997). This spice principle inhibited the formation of arachidonate metabolites (PgE2, leukotrienes) and increased the secretion of lysosomal enzymes - elastase, collagenase and hyaluronidase by macrophages. It is noteworthy that the levels of 6-keto PgF1a - a vasodilator increased (Joe and Lokesh, 1997a).

The signaling mechanism underlying the anti-inflammatory action of capsaicin, was investigated wherein the effect of capsaicin on the production of inflammatory molecules in lipopolysaccharide (LPS)-stimulated murine peritoneal macrophages (Kim et al., 2003). The results suggested that the anti-inflammatory action of capsaicin may occur through a novel mechanism, other than by a VR-1 receptor-mediated one. Natural anti-inflammatory compound capsaicin appear to operate by inhibiting one or more of the steps linking pro-inflammatory stimuli with COX activation, such as the blocking by capsaicin of NF-kB translocation into the nucleus (Surh et al., 2005). It has been shown recently that the natural anti-inflammatory compounds such as capsaicin were as effective as indomethacin (a non-steroidal anti-inflammatory drug) in inhibiting aberrant crypt foci in the rat.

CHEMOPREVENTIVE ACTIVITY OF CAPSAICIN

Capsaicin has been studied widely for its chemopreventive properties. Capsaicin exhibits antigrowth activity against various cancer cell lines. However, the role of capsaicin in tumorigenesis remains controversial because both cancer prevention and promotion have been proposed (Liu et al., 2012). Hence caution should be taken when using capsaicin as a chemopreventive agent.

Capsaicin has been found to interact with microsomal xenobiotic metabolizing enzymes in rodents. Capsaicin has been proposed to inactivate cytochrome P-450 HE1 by irreversibly binding to the active sites of the enzyme (Surh et al., 1995). Besides cytochrome P-450 HE1, other isoforms of the P-450 super family are also reported to be inhibited by capsaicin. The inhibition by capsaicin of microsomal mono-oxygenases involved in carcinogen activation implies its chemopreventive potential. The anti-tumor activity of capsaicin against benzo(Ŭ) pyrene-induced lung tumorigenesis has been reported in mice (Anandakumar et al., 2012). Capsaicin (10 mg/kg body weight) supplementation to lung cancer bearing mice considerably prevented all the abnormalities in lung cancer-challenged mice administered with benzo(Ŭ)pyrene. The results of the present study indicate the protective effect of capsaicin against benzo(a)pyrene-induced lung carcinogenesis in mice.

Studies suggest that capsaicin is able to kill prostate cancer cells by causing apoptosis (Mori et al., 2006). The studies were performed on tumors formed by human prostate cancer cell cultures grown in mouse models, and showed tumors treated with capsaicin were about one-fifth the size of the untreated tumors. There have been several clinical studies conducted in Japan and China that showed capsaicin directly inhibits the growth of leukemic cells (Ito et al., 2004). Another study suggests capsaicin is able to trigger apoptosis in human lung cancer cells as well (Lee et al., 2010).

ANTI-DIABETIC POTENTIAL

Substance P, a neuropeptide released by capsaicin, has been shown to reverse diabetes in mice (Tsui et al., 2007), but the effects to insulin secretion seem to be species dependent. In humans, substance P seems to decrease insulin release and cause fluctuations in blood sugar levels (Brown and Vale, 2011). Capsaicin is also being explored as a possible prophylaxis for Type 1 diabetes. Capsaicin was injected subcutaneously in neonatal diabetes-prone NOD mice to permanently remove a prominent subset of pancreatic sensory neurons, which express the transient vanilloid receptor protein (TRPV1). Insulin resistance and ϐ-cell stress of prediabetic NOD mice are prevented when TRPV1+ neurons are eliminated. In other words, mice which were genetically predisposed to Type 1 diabetes were prevented from developing Type 1 diabetes via removal of these neurons, which are thought to attract pathogenic T-cells to attacking pancreatic ϐ-cells thus causing Type 1 diabetes (Razavi et al., 2006).

THERMOGENIC AND WEIGHT REDUCING INFLUENCE OF CAPSAICIN

According to animal and human studies, the oral intake of capsaicin increases the production of heat by the body for a short time. Dietary red pepper or its pungent principle capsaicin affect satiety and have a promising thermogenic influence that could play an important role in the prevalence and severity of obesity (Kawada et al., 1986), although more data are required to substantiate this benefit. The use of this spice to displace fats and salt in the diet (to make the food palatable) may reduce cardiovascular risk. Although there is no evidence showing that weight loss is directly correlated with ingesting capsaicin, there is a positive correlation between ingesting capsaicin and a decrease in weight regain. Capsaicin is said to cause a shift in substrate oxidation from carbohydrate to fat oxidation (Lejeune et al., 2003) which leads to a decrease in appetite as well as a decrease in food intake. Both oral and gastrointestinal exposure to capsaicin increases satiety and reduces energy as well as fat intake (Westerterp-Plantenga et al., 2004). Oral exposure proves to yield stronger reduction suggesting that capsaicin has sensory effects. Short-term studies suggest that capsaicin aids in the decrease of weight regain. However, long-term studies are limited because of the pungency of capsaicin (Diepvens et al., 2007). Another recent study has suggested that the ingestion of capsaicinoids can increase levels of brown adipose tissue through an increase in energy expenditure and oxidation caused by the capsaicin (Yoneshiro et al., 2012). In yet another recent study, the beneficial effects of dietary tender cluster beans (*Cyamopsis tetragonoloba*) in checking the weight gain and adverse changes in lipid profile in high-fat fed condition were potentiated by co-administration of capsaicin in rats (Pande and Srinivasan, 2012).

ANTI-ULCER ACTIVITY OF CAPSAICIN

In recent years, infection of the stomach with *Helicobacter pylori* which disrupts the normal inhibitory control for acid secretion resulting in excess acid destroying the mucosal barrier, has been understood to be the main cause of gastric ulcers (López-Carrillo et al., 2003). Excessive acid secretion in the stomach and reduction in gastric mucosal blood flow are considered responsible for ulcer formation. The colonization of *H. pylori* in the stomach is associated with a phospholipase likely to damage the protective layer of stomach. *H. pylori* thrives in the stomach by producing the enzyme urease.

In view of its irritant and likely acid secreting nature, persons with ulcers were being advised to avoid consumption of red pepper (chili). However, recent studies have revealed that capsaicin of red pepper is not the cause for ulcer formation but a benefactor. Numerous studies suggest that eating hot peppers regularly is protective against stomach cancer (Buiatti et al., 1989). Detailed studies have revealed that capsaicin *per se* does not stimulate but inhibits acid secretion, stimulates alkali and mucus secretions and gastric mucosal blood flow which help in disposing of acid from the stomach, thus prevention and healing of ulcers (Satyanarayana, 2006). Capsaicin acts by stimulating afferent neurons in the stomach and signals for protection against injury causing agents. An epidemiological study has found 3-times higher peptic ulcer incidence among Chinese population in Singapore as compared to Malaysians and Indians who are in the habit of consuming more pungent chili in their daily diets (Kang et al., 1995).

Interestingly, capsaicin has been found to specifically inhibit the growth of *H. pylori*. Capsaicin inhibits also the release of gastrin and stimulates that of somatostatin, the physiological inhibitor of acid secretion. It is also a potent inhibitor of NF-kB whose activation may lead to various pathological conditions and reactive oxygen species. Phosphodiesterase inhibitors are powerful vasodilatory agents and their likely increase of cAMP levels has an anti-ulcer effect. Capsaicin is a phosphodiesterase inhibitor and may exert its protective effect in this way besides its stimulation of gastric mucosal blood flow. Numerous studies have substantiated the protective role of capsaicin. Seminal to these studies is the discovery about the selective sensitization and desensitization of unmyelinated neurons by capsaicin (Jancso et al., 1977). Reactive oxygen species are known to be involved in the pathogenesis of gastritis, gastric ulcers, and gastric cancer. Capsaicin has proved to be an antioxidant protecting cellular membranes, cardiac and skeletal muscles, etc. against reactive oxygen species. Capsaicin inhibited lipid peroxidation induced by ethanol in the gastric mucosa (Park et al., 2000).

CAPSAICIN IN PAIN RELIEF

Capsaicin has received considerable attention as a pain reliever. In two trials with 70 and 21 patients with osteoarthritis and rheumatoid arthritis, topical application of creams containing 0.025% or 0.075% capsaicin was an effective and safe alternative to analgesics employed in systemic medications which are often associated with potential side effects (Deal, 1991; McCarthy and McCarthy, 1991). Capsaicin has also been suggested for the initial management of neuralgia consequent to herpes infection (Bernstein, 1989).

Capsaicin has been shown to be useful in diabetic neuropathy. In a study involving 219 patients, topical application of 0.075% capsaicin cream was effective in pain management (The Capsaicin Study Group, 1992). Capsaicin is currently used in topical ointments, as well as a high-dose dermal patch (under the trade name ó*Qutenza*ô), to relieve the pain of peripheral neuropathy such as post-herpetic neuralgia caused by shingles (Derry et al. 2009). It may be used in concentrations of between 0.025% and 0.075% as a cream for the temporary relief of minor aches and pains of muscles and joints associated with arthritis, simple backache, strains and sprains, often in combination with other rubefacients (Derry et al., 2009). Capsaicin creams are used to treat psoriasis as an effective way to reduce itching and inflammation (Glinski et al., 1991, Arnold and van de Kerkhof, 1993). Capsaicin is also the key ingredient in the experimental drug ó*Adlea*ô, which is in Phase 2 trials as a long-acting analgesic to treat post-surgical and osteoarthritis pain (Derry et al., 2009). Moreover, it reduces pain resulted from rheumatoid arthritis (Fraenkel et al., 2004) as well as joint or muscle pain from fibromyalgia.

Over-the-counter capsaicin creams have however shown moderate to poor analgesic efficacy. This is in part related to low dose, poor skin absorption, and compliance factors. Recently developed site-specific capsaicin therapy with high-dose patches and injectable preparations reportedly provide long-lasting analgesia with rapid onset. Safety and modest efficacy of low-concentration capsaicin formulations, which require repeated daily self-administration, are supported by meta-analyses of numerous studies. A single 60-min application of a high-concentration capsaicin 8% patch (QutenzaÊ) in patients with neuropathic pain produced

effective pain relief for up to 12 weeks (Anand and Bley, 2011). Advantages of the high-concentration capsaicin patch include longer duration of effect and low risk for systemic effects.

The current understanding of the molecular basis for pain relief by capsaicin (TRPV1 agonist) is explained (Knotkova et al., 2008). The capsaicin receptor TRPV1 is a polymodal nociceptor exhibiting a dynamic threshold of activation that could be lowered under inflammatory conditions. The mechanism of action of topical capsaicin has been ascribed to depletion of substance P. However, experimental and clinical studies show that depletion of substance P from nociceptors is only a correlate of capsaicin treatment and has little, if any, causative role in pain relief. Rather, topical capsaicin acts in the skin to attenuate cutaneous hypersensitivity and reduce pain by a process best described as 'defunctionalization' of nociceptor fibres. Peripheral neuropathic hypersensitivity is mediated by diverse mechanisms, including altered expression of the capsaicin receptor TRPV1 or other key ion channels in affected or intact adjacent peripheral nociceptive nerve fibres, aberrant re-innervation, and collateral sprouting, all of which are defunctionalized by topical capsaicin.

BENEFICIAL INFLUENCES ON GASTRO INTESTINAL SYSTEM

1) Beneficial modulation of small intestinal ultra structure

The beneficial influence of dietary capsaicin has been examined in experimental rats w.r.t. (i) the membrane fluidity of intestinal brush-border membranes (BBM), (ii) the activity of intestinal membrane-bound enzymes, and (iii) ultra structural alterations in the intestinal epithelium

(Prakash and Srinivasan, 2010). In this study, Wistar rats were maintained on dietary red pepper (3·0 %) and its bioactive compound capsaicin (0·01 %) for 8 weeks. A membrane fluidity study using an apolar fluorescent probe showed increased BBM fluidity in the spice-fed or capsaicin fed animals. This was corroborated by decreased cholesterol: phospholipid ratio in the jejunal and ileal regions of the intestine. These dietary spices stimulated the activities of BBM enzymes (glycyl-glycine dipeptidase, leucine amino peptidase and ɔ-glutamyl transpeptidase) in the jejunal mucosa, suggesting a modulation in membrane dynamics due to the apolar spice bioactive compound interacting with surrounding lipids and hydrophobic portions in the protein vicinity, which may decrease the tendency of membrane lipids to act as steric constraints to enzyme proteins and thus modify enzyme conformation. Scanning electronic microscopy of the intestinal villi in these spice treatments revealed alterations in the ultra structure, especially an increase in microvilli length and perimeter which would mean a beneficial increase in the absorptive surface of the small intestine, providing for an increased bioavailability of micronutrients. Thus, dietary red pepper or capsaicin were evidenced to induce alterations in BBM fluidity and passive permeability property, associated with the induction of an increased microvilli length, resulting in an increased absorptive surface of the small intestine.

2) Digestive stimulant action of capsaicin

The digestive stimulant action of spices is probably exerted through stimulation of the liver to produce and secrete bile rich in bile acids, which play a very important role in fat digestion and absorption. Capsaicin has been examined for its effect on bile secretion in rats, after dietary

intake for a period of time or as a one-time oral intake (Bhat et al., 1884). The hypo-cholesterolemic spice compound capsaicin stimulated bile acid production by the liver and its secretion into bile. The influence of dietary intake and single dose administration of capsaicin on the pancreatic digestive enzymes and the terminal digestive enzymes of the small intestinal mucosa have been reported (Platel and Srinivasan, 1996, 2000). Dietary intake of capsaicin stimulated pancreatic lipase activity significantly. In contrast to the continued intake, single oral dose consumption of capsaicin failed to exert a stimulatory effect on pancreatic lipase. Pancreatic amylase activity was elevated by dietary capsaicin (72%) as well as single dose administration of capsaicin. Capsaicin when incorporated in the diet, stimulated trypsin activity by over 100%. Chymotrypsin was also significantly higher in animals fed capsaicin. Similar influence of the spice compound on the activity of proteases was not evident when administered as a single oral dose. Capsaicin prominently enhanced the activity of intestinal lipase. The stimulation of this enzyme activity was more than 100% of the control in spice principle-treated group. Similarly, dietary capsaicin significantly increased the activity of intestinal amylase. Dietary capsaicin moderately stimulated the activities of intestinal disaccharidases.

Based on the evidences from animal studies, the well recognized digestive stimulant action of red pepper or its active compound capsaicin may be considered to be mediated through two possible modes (i) stimulation of the liver to secrete more bile enriched in bile acids, and (ii) stimulation of enzyme activities that participate in digestion, both of pancreatic and intestinal origin. Such stimulation of bile secretion and of the activities of digestive enzymes leads to an

accelerated overall digestive process, resulting in a significant reduction in the duration of passage of food through the gastrointestinal tract (Platel and Srinivasan, 2001).

Since capsaicin is known to stimulate secretion of bile with higher amount of bile acids which play a major role in digestion and absorption of dietary lipids, capsaicin has been studied to verify if it enables efficient digestion and absorption during high-fat intake (Prakash and Srinivasan, 2012). In this context, dietary capsaicin (0.015%) has been examined for its influence on bile secretion, digestive enzymes of pancreas and absorption of dietary fat in high-fat (30%) fed rats for 8 weeks. Dietary capsaicin enhanced the activity of pancreatic lipase, amylase, trypsin and chymotrypsin, and enhanced dietary fat absorption. It also increased bile secretion with higher bile acid content. Stimulation of lipid mobilisation from adipose tissue was suggested by the decrease in perirenal adipose tissue weight by dietary capsaicin. This was also accompanied by prevention of the accumulation of triglyceride in liver and serum in high-fat fed rats. Activities of key lipogenic enzymes in liver were reduced which was accompanied by an increased activity of hormone-sensitive lipase. Thus, dietary capsaicin enhances fat digestion and absorption in high-fat fed situation through enhanced secretion of bile salts and a stimulation of the activity pancreatic lipase. At the same time, the energy expenditure is facilitated by this spice compound to prevent the accumulation of absorbed fat.

3) Enhanced absorption of micronutrients

Since dietary pungent spices may alter the ultra structure and permeability characteristics of intestines, capsaicin has been examined for a possible influence on intestinal absorption of iron, zinc and calcium by examining their uptake by the intestines from rats pre-fed spice compound for 8 weeks (Prakash and Srinivasan, 2012a). Everted segments of duodenum, jejunum and ileum portions of small intestines isolated from these rats were examined for *ex vivo* uptake of iron, zinc and calcium from incubations containing digesta of finger millet. Higher *in vitro* absorption of iron, zinc and calcium in the intestines was evidenced in capsaicin-fed animals. The positive influence of dietary capsaicin on the mineral uptake by the intestinal segments was highest for calcium. The positive influence of dietary capsaicin was more pronounced on zinc uptake as compared to that of iron. These pungent spices alter permeation characteristics presumably by increasing absorptive surface, and thereby enhance intestinal absorption of micronutrients.

Dietary red pepper and capsaicin which alter the ultra structure and permeability characteristics of intestines are also reported to favourably enhance the intestinal uptake of ß-carotene *in vitro* (Veda and Srinivasan, 2008). In an animal study conducted to evaluate the influence of dietary spice compounds on the absorption of orally administered ß-carotene and its conversion to vitamin-A, hepatic ß-carotene was significantly increased in capsaicin-fed rats suggesting improved absorption of ß-carotene (Veda and Srinivasan, 2011). Retinol concentration was not however changed in these animals suggesting that bioconversion of ß-carotene to vitamin-A was not similarly influenced. Among the two enzymes involved in the bioconversion of ß-carotene to vitamin-A, activity of intestinal and hepatic ß-carotene-15,15ô-dioxygenase was lowered in capsaicin treatment, while the activity of intestinal and hepatic

retinal reductase was unaffected. Activity of intestinal and hepatic ß-carotene-15,15ô-dioxygenase was also inhibited by capsaicin *in vitro*, thus corroborating with *in vivo* observation.

MECHANISM OF BURNING AND PAINFUL SENSATION OF CAPSAICIN

Capsaicin causes a burning sensation when it comes in contact with mucous membranes. The burning and painful sensations associated with capsaicin result from its chemical interaction with sensory neurons. Capsaicin, as a member of the vanilloid family, binds to a vanilloid receptor (TRPV1) (Story and Crus-Orengo, 2007), an ion channel-type receptor that resides on the membranes of pain and heat sensing neurons (Caterina et al., 1997). VR1, which can also be stimulated with heat and physical abrasion, permits cations to pass through the cell membrane and into the cell when activated. The resulting depolarization of the neuron stimulates it to signal the brain. By binding to the VR1 receptor, the capsaicin molecule produces the same sensation that excessive heat or abrasive damage would cause.

The TRPV1 ion channel has been shown to be a member of the super family of TRP ion channels. There are a number of different TRP ion channels that have been shown to be sensitive to different ranges of temperature. Thus, capsaicin does not actually cause a chemical burn, or indeed any direct tissue damage at all, consequent to exposure to chili peppers. The inflammation resulting from exposure to capsaicin is believed to be the result of the body's reaction to nerve excitement. TRPV1 is a heat activated calcium channel, which opens between 37 and 45 °C. When capsaicin binds to TRPV1, it causes the channel to open at temperature below 37 °C

(normal human body temperature), which is why capsaicin is linked to the sensation of heat. Prolonged activation of these neurons by capsaicin depletes presynaptic substance P, one of the body's neurotransmitters for pain and heat. Neurons that do not contain TRPV1 are unaffected. Thus, capsaicin mimics a burning sensation, the nerves being overwhelmed by the influx. Capsaicin will be unable to evoke pain for an extended period of time since with chronic exposure, neurons are depleted of neurotransmitters, leading to reduction in sensation of pain and blockade of neurogenic inflammation. If capsaicin is removed, the neurons recover (Geppetti et al. 2008, Kissin 2008). The mode of action of capsaicin in inducing broncho-constriction is thought to involve stimulation of C fibre culminating in the release of neuropeptides (Fuller et al., 1985). Essentially, the body inflames tissues as if it has undergone a burn or abrasion and the resulting inflammation can cause tissue damage in cases of extreme exposure.

ABSORPTION AND METABOLISM OF CAPSAICIN

Capsaicin fed to rats was rapidly absorbed from the stomach, with 85% of a 3 mg dose absorbed within 3 h (Toth and Gannett, 1992). Doses of 5.12 mg/mouse/week led to maximum plasma concentrations of 51.5 ng/mL and 84.8 ng/mL in male and female mice, respectively (Philip et al., 1994). Little absorption of capsaicin also occurs across the skin. When 0.8 g of gel containing 0.075% of capsaicin was applied to the skin of human volunteers, the average absorbed dose after 8 h of exposure was 22.7 $\mu g/cm^2$ (Kawada et al., 1984). Topical application of pure capsaicin to the skin of mice resulted in peak plasma concentrations occurring 4 to 12 h later, and capsaicin was detectable in the blood 24 h after dosing (Philip et al., 1994).

Rats injected intravenously accumulated capsaicin primarily in the brain and spinal cord 3 min after dosing, with lower levels found in the liver and blood, while 10 min after dosing, the greatest concentrations remained in the spinal cord (Akagi et al., 1998). Subcutaneously injected capsaicin was detected in all tissues of rat 10 min following dosing but residues were undetectable in any tissues 17 h later. Blood concentrations peaked 5 h following dosing, and brain and spinal cord tissue concentrations were somewhat lower. Kidneys contained the greatest concentrations and liver concentrations were low presumably due to metabolic breakdown of the capsaicin (Akagi et al., 1998). Tissue distribution and elimination of capsaicin has been examined following its oral intake (30 mg capsaicin/kg body weight) in rats (Suresh & Srinivasan 2010). Maximum distribution of 24.4% of administered capsaicin was seen at 1 h, while no intact capsaicin was detectable after 4 days. Absorption of capsaicin was about 94% and very rapid.

Less than 10% of an oral dose of capsaicin given to rats was excreted unchanged 48 h after dosing (Toth et al., 1992). Metabolism of capsaicin occurs primarily in the liver in the rat (Richeux et al., 1999; Chanda et al., 2006). Although the same metabolites were produced, the relative amounts of each metabolite were species-dependent. Metabolism of capsaicin by P450 enzymes may follow a number of pathways and produce a variety of metabolites, some of which may be associated with increased toxicity (Reilly and Yost, 2006). A recent study characterized electrophilic and radical products derived from the metabolism of capsaicin by cytochrome P-450 and peroxidase enzymes (Reilly et al., 2012). The study demonstrated that capsaicin is

converted to reactive intermediates by certain P450 enzymes, which may partially explain conflicting reports related to the cytotoxic, pro-carcinogenic, and chemoprotective effects of capsaicinoids in different cells and/or organ systems.

SAFETY OF CONSUMPTION OF RED PEPPER OR CAPSAICIN

Consumed worldwide, capsaicin has a long history of controversy about whether its consumption or topical application is entirely safe. Conflicting epidemiologic data and basic research study results suggest that capsaicin can act as a carcinogen or as a cancer preventive agent. Though not so extensively, limited safety evaluation study has been done on red pepper which indicated that even at several times normal human intake among Indian population, red pepper has no adverse effects on growth, organ weights, feed efficiency ratio, nitrogen balance, and blood chemistry (Sambaiah et al., 1982). Employing reliable validated mammalian assays, it was conclusively demonstrated that capsaicin did not induce any mutagenic effects *in vivo* either in the somatic or germ cells in mice (Muralidhara and Narasimhamurthy, 1988).

Capsaicin is unique among naturally occurring irritant compounds because the initial neuronal excitation evoked is followed by a long-lasting refractory period, referred to as desensitization and has been exploited for its therapeutic potential. Capsaicin-containing creams have been in clinical use for many years to relieve a variety of painful conditions. However, their effectiveness in pain relief is also highly debated and some adverse side effects have been

reported. We have found that chronic, long-term topical application of capsaicin increased skin carcinogenesis in mice treated with a tumor promoter such as sunlight (Bode and Dong, 2011).

Known side effects of using capsaicin in the diet and pain relief cream:

Although animal studies have shown no or minimal side effects, capsaicin is feared to cause skin irritation, neurotoxicity, and systemic adverse effect in humans. Capsaicin causes stinging pain to the skin, and if ingested in large amounts, can produce nausea, vomiting, abdominal pain and burning diarrhoea. Eye exposure produces intense tearing, pain, conjunctivitis and blepharospasm (Goldfrank, 2002). Capsaicin is a powerful irritant; initial administration causes intense pain. Prolonged treatment causes insensitivity to painful stimuli and induces selective degeneration of certain primary sensory neurons (OôNeil, 2001). Capsaicin is considered a moderate irritant to human skin and a strong irritant to gastric mucosa. Irritating to mucous membranes; produces severe gastritis and diarrhoea (Lewis, 2004). Early studies with topical capsaicin involved the use of 1% capsaicin. At this concentration, capsaicin is a neurotoxin and produces destruction (Fitzgerald, 1983). A 1% topical capsaicin in man produces thermal hyperalgesia (Carpenter and Lynn, 1981). No evidence of dermal toxicity exists with lower levels of topical capsaicin which still have beneficial effects. There is some concern that capsaicin may be potentially neurotoxic. Capsaicin is thought to be capable of elevating the heat pain threshold in the treated skin areas, especially in patients with diabetic neuropathy; these patients often already have an elevated threshold for heat and pain (Thomson/Micromedex, 2006). An unusual case of gastroenteritis due to excessive consumption of chillies has been reported (Bartholomew

and Carlson, 1994). Allergic reactions to capsaicin have also been documented (Poller and Cacroix, 1993).

CONCLUSIONS

Several of the biological effects of capsaicin which are of pharmacological relevance have been studied extensively. These include: thermogenic influence, effects on gastrointestinal system, cardio protective influence, anti-lithogenic effect, anti-inflammatory and pain relieving effect. The involvement of neuropeptide Substance P, serotonin, somatostatin and calcitone gene related peptide in the pharmacological actions of capsaicin has been extensively investigated. Tropical application of capsaicin has been proved to alleviate pain in arthritis, post-operative neuralgia, diabetic neuropathy, psoriasis, etc. Toxicological studies on capsaicin administered by different routes are documented. Capsaicin inhibits acid secretion, stimulates alkali and mucus secretion, and particularly stimulates gastric mucosal blood flow which helps in prevention and healing of gastric ulcers. Antioxidant and anti-inflammatory properties of capsaicin are established in a number of *in vitro* and *in vivo* studies. Chemopreventive potential of capsaicin has been evidenced in a few animal and cell line studies. The health beneficial hypocholesterolemic influence of capsaicin is not only cardio protective; besides it has other implications, viz., prevention of cholesterol gallstone disease and protection of the structural integrity of erythrocytes under conditions of hypercholesterolemia. Beneficial influences of capsaicin on gastrointestinal system includes: digestive stimulant action and beneficial modulation of small intestinal ultra structure so as to enhance permeability to micronutrients.

In view of the promising anti-inflammatory potential of capsaicin and also its thermogenic property which is of significance in weight management, capsaicinoids merit exploitation for human health benefits. However, due to its extreme pungency and irritational characteristics capsicum extracts or capsaicin have not been used to any significant extent for their medicinal effects as yet. Hence there is a need to develop non-pungent forms of extracts of capsicum and also modes of non-irritant pharmaceutical delivery. In other words, suitable encapsulation of the pungent extracts or capsaicin is required to be developed. Such derivatives would facilitate human trials for validation of diverse health benefits, which at present is limited to human studies on capsaicin as a pain relief agent and also lead to pharmaceutical application of this pungent compound.

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Table-1. Hypolipidemic effect of red pepper (*Capsicum annuum*)/ capsaicin in experimental animals

Animal Model	Effect demonstrated	Reference
Rats on 40% fat	5% red pepper or 0.015% capsaicin lowered serum & liver cholesterol	Sambaiah *et al*. 1978
Rats	1.5, 3 and 15 mg% capsaicin reduced serum cholesterol	Srinivasan *et al*. 1980
Rats on 10 or 30% fat	0.2% capsaicin effectively lowered serum cholesterol	Srinivasan & Satyanarayana 1987
Rats	Subchronic levels of capsaicin (50 mg/kg for 60 days) lowered cholesterol & triglycerides	Monsereenusorn 1983
Rats on 30% lard	14 mg% capsaicin produced hypocholesterol-emic effect	Kawada *et al*. 1986
Rats on 1% cholesterol	Effective hypocholesterolemic effect; Higher excretion of fecal sterols and bile acids	Sambaiah & Satyanarayana 1980
Rats on 0.5% cholesterol	15 mg% capsaicin produced anti-hypercholesterolemic effect	Kempaiah & Srinivasan 2002
Diabetic Rats	15 mg% dietary capsaicin did not reverse hypercholesterolemia & hypertriglyceridemia	Babu & Srinivasan 1997
Hypercholesterolemic Rats	Dietary capsaicin stimulated activity of hepatic cholesterol-7α-hydroxylase	Srinivasan & Sambaiah 1991
Hypercholesterolemic Rabbits	Reduced blood cholesterol, triglycerides	Negulesco *et al*. 1983
Hypercholesterolemic Turkeys	Reduced blood cholesterol; ameliorated aortic atherosclerotic lesions by capsaicin	Ki *et al*. 1982, Negulesco *et al*. 1987
Gerbils	75 mg oleoresin/kg decreased blood cholesterol & triglycerides; Prevented lipid accumulation in liver and aorta	Gupta *et al*. 2002

Table-2. Antioxidant influence of Red pepper and Capsaicin

Animal model	Effect demonstrated	Reference
Human erythrocyte membranes	Lipid peroxidation was inhibited by capsaicin	Salimath *et al*., 1986
Rat liver microsomes	Ascorbate-Fe^{++}-induced lipid peroxidation was inhibited by capsaicin	Reddy & Lokesh, 1992
Soybean phospholipid liposomal membrane	Inhibition of oxidation of methyl linoleate micelles by capsaicin	Okada & Okajima, 2001
Rat liver mitochondria	Inhibition of lipid peroxidation induced by ADP/ Fe^{2+} and scavenging of DPPH radicals by capsaicin	Kogure *et al*, 2002
Human low density lipoprotein	Inhibition of Cu^{2+} induced lipid peroxidation by capsaicin	Naidu & Thippe-swamy, 2002
Human PMNL cells	Inhibition of 5-lipoxygenase	Prasad *et al*, 2004
Rats	Capsaicin administration reduced oxidative stress	Lee *et al*, 2003

	in the liver, lung, kidney and muscle	
High fat fed rats	Beneficial influence of dietary capsaicin on anti-oxidant status of red blood cells	Kempaiah & Srinivasan, 2004a
Hypercholesterolemic rats	Beneficial influence of dietary capsaicin on anti-oxidant status of red blood cells	Kempaiah & Srinivasan, 2004b

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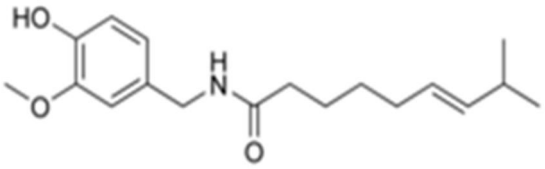
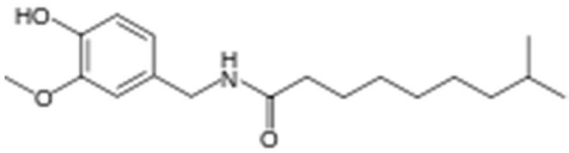
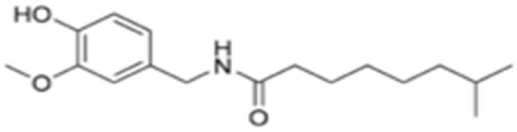
Red pepper (chili)



Capsaicin (69%)



Dihydrocapsaicin (22%)



Nordihydrocapsaicin (7%)

Fig.1. Red pepper and major capsaicinoids

ACCEPTED MANUSCRIPT

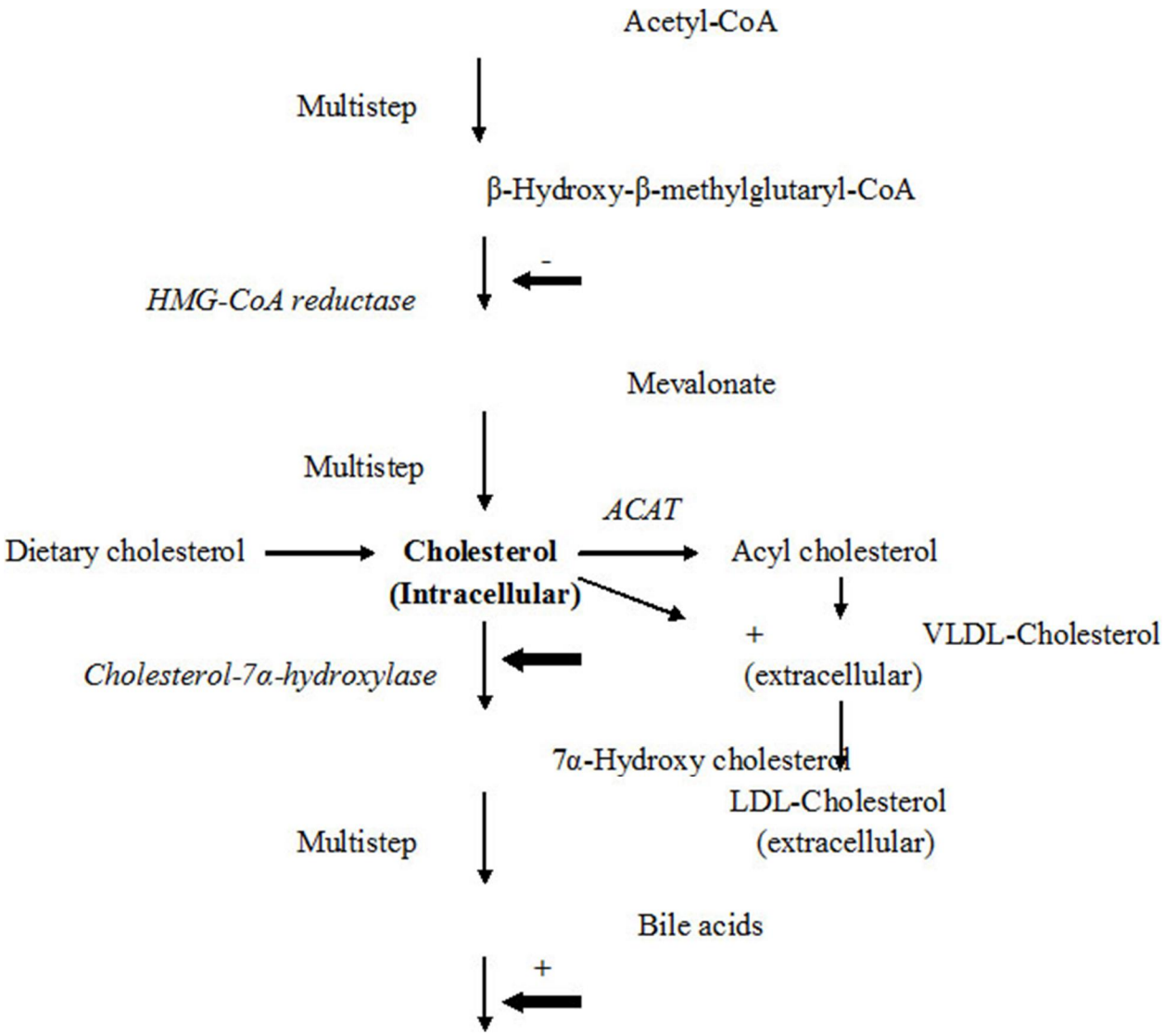


Fig.2. Beneficial modulation of cholesterol homeostasis by dietary capsaicin by: (a) Inhibition of *de novo* synthesis in liver, (b) Stimulation of conversion to bile acids in liver, and (c) Higher secretion of bile acids into bile

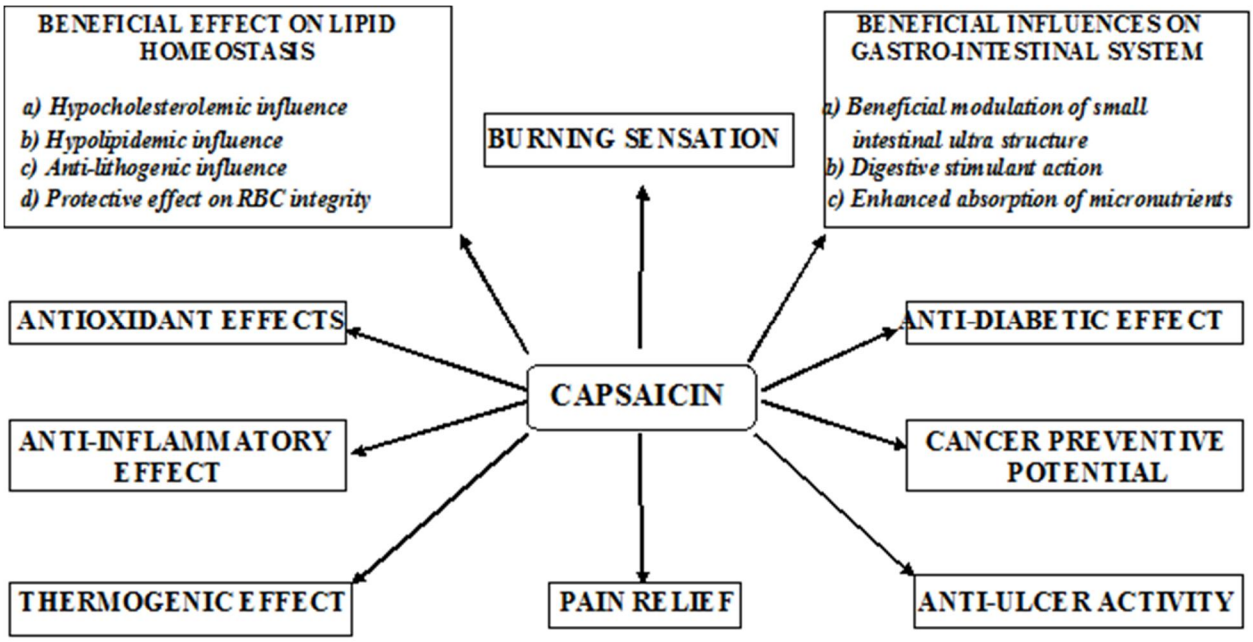


Fig.3 Summary of the diverse physiological effects of capsaicin