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REVIEW ARTICLE

Dietary, Anticancer and Medicinal Properties of the Phytochemicals in Chili Pepper (*Capsicum* spp.)

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Abstract: Chili pepper (*Capsicum* spp.) is important as a spice, flavour enhancer, vegetable and component in herbal medicine. The numerous phytochemicals and their medicinally important properties present in diverse germplasm of chili pepper have been characterized and documented. Capsaicinoids, carotenoids, vitamins, flavonoids such as anthocyanins are present as the major phytochemicals in chili pepper fruits. Capsaicinoids, pungent analogues of capsinoids, are the most important group of phytochemicals in which capsaicin and dihydrocapsaic in are prominent in providing the basis for pungency and medicinal properties. The detailed studies conducted on the phytochemicals in chili pepper fruits using mouse models and human cell lines have reported an array of anticancer effects on leukemia, myeloma and various carcinomas associated with the digestive tract. In addition, chili pepper possesses anti-inflammatory, antidiabetic, antimicrobial, anticholesteremic, anticlotting and antioxidant activities. Therefore, this review is compiled to provide a comprehensive assessment of the phytochemical profile and medicinal values of chili pepper. Collectively, numerous studies performed to date demonstrated the potential medicinal significance of chili pepper for development of herbal medicine and to plan further studies to elucidate other hitherto unknown medicinal values.

Keywords: *Capsicum*, Capsaicin, Capsaicinoids, Phytochemicals, Anticancer activity

INTRODUCTION

Chili pepper, (*Capsicum* spp.), is an essential element in our daily cuisine. It is the most highly consumed spice in the world with a mean annual consumption of 3.5 million metric tons of dried fruit (FAO, 2015).Characteristic pungency and flavour of the chili pepper fruits provide unique hotness to meal preparations and a wide variety of foods utilize this pungency in combination with salt and other spices for flavour enhancement (Pino *et al*., 2007). The genus *Capsicum* is highly diverse and contains 40 species (The Plant List, 2013). Of those, five species, *C. annuum var. annuum, C. chinense, C. frutescens, C. baccatum* varieties *pendulum* and *umbilicatum* and *C. pubescens* are most frequently consumed by humans (Moscone *et al*., 2007). The domestication of chili pepper has been dated to 6000 B.C., and archeological evidence (genus specific starch-granule-morphotypes) found in the Bahamas and Southern Peru imply that chili pepper had been a component in diets as early as in 7500 B.C. (Perry, 2007).

Apart from the culinary uses, chili pepper has also been used in medicinal preparations, providing nutritional and health advantages such as anticancer, anti-inflammatory, antidiabetic, anticholesteremic, anticlotting, analgesic and antimicrobial effects. Mayans used chili pepper to treat microbial diseases (Cichewicz and Thorpe, 1996) and many reports from India show that chili pepper was used to treat asthma (even the chili root extracts were used), gastrointestinal tract problems (Baruah *et al*., 2014), extreme pain, toothache, wounds, ulcers, arthritis (Bhagowati and Changkija, 2009), headaches and night blindness (Deorani and Sharma, 2007). Treating hypersensitivity and rheumatism using chili pepper also was common

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in Italian indigenous medical practices (Pieroni *et al*., 2004).

The indigenous uses of chili pepper in folk medicinal applications and the safe and prolonged use of chili pepper as a spice in human history enable us to think that the phytochemicals present in chili pepper fruits promote and maintain the good health of human beings (Bosland, 1996). These phytochemicals and their nutritional and medicinal values have been characterized in numerous studies. A few reviews have been published on metabolism and bioavailability (Rollyson *et al*., 2014) and anticancer effects (Cao *et al*., 2015; Pawar *et al*., 2011) of capsaicin and nutraceutical benefits of chili pepper in general (Milind and Sushila, 2012). However, the array of medicinal properties in chili pepper has not been reviewed together to realize it's multiple roles. This paper reviews the medicinal values of chili pepper on diverse ailments including cancer, diabetics, cholesteromia and microbial infections.

PHYTOCHEMICAL PROFILE

The phenolic compounds present in the chili pepper are attributed to many medicinally important properties such as anti-diarrheal, antimicrobial, antioxidant, antihyperglycemic, anti-lithogenic and antimutagenic activities (Adefegha and Oboh, 2013). Chili pepper fruits contain phenolic compounds such as flavonoids (Chu *et al*., 2002), β-catenin, capsaicinoids (Vera-Guzman *et al*., 2011), carotenoids (capsanthin, capsorubin and cryptocapsin), vitamins A, B, C and E (Kidmose *et al*., 2006; Niizu and Rodriguez-Amaya, 2005; USDA Nutrient Data Laboratory, 2015), glycolipids, glycerolipids and esters (Bijttebier *et al*., 2014).

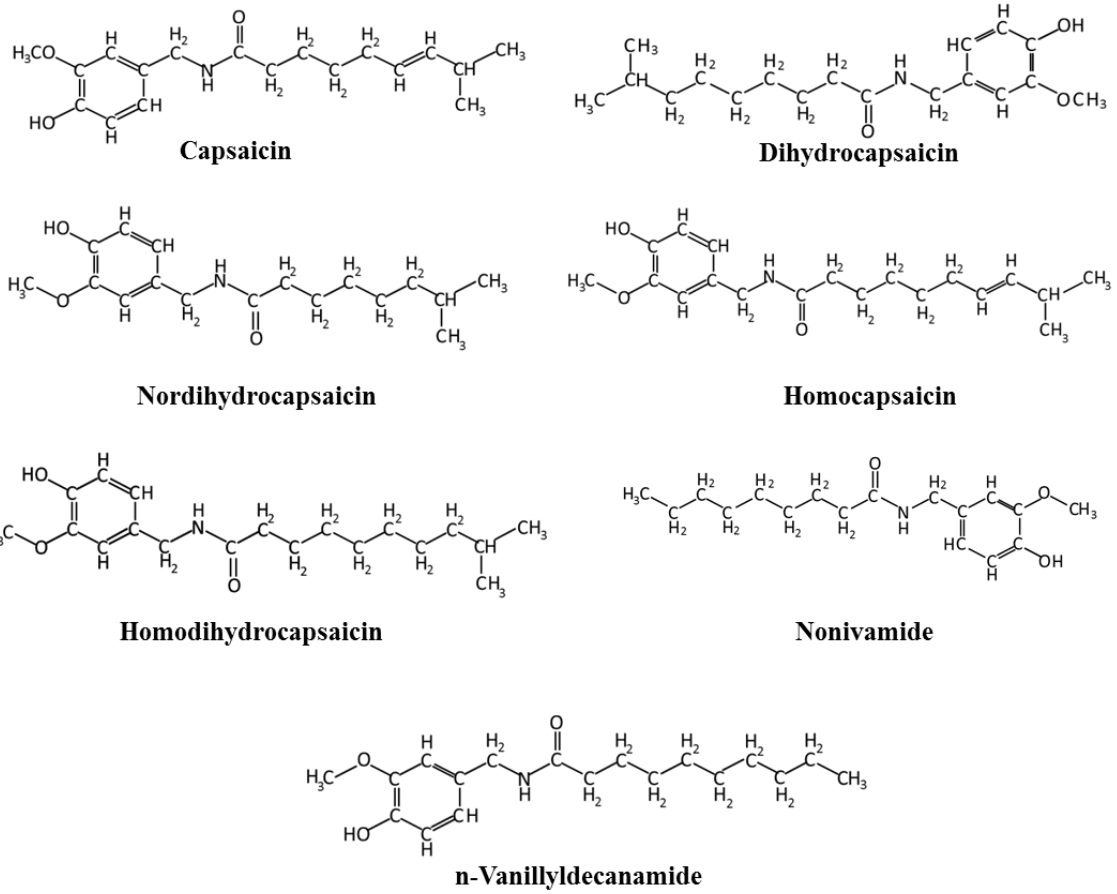

Figure 1: The structures of the common capsaicinoids in chili pepper.

Chemical composition of chili pepper fruit extracts has been characterized using GC/MS spectrophotometry (Wesolowska *et al*., 2011) and liquid chromatography-photodiode array-accurate mass mass spectrometry (LC-PDA-amMS) (Bijttebier *et al*., 2014). There are five major capsaicinoids observed in chili pepper (capsaicin, homocapsaicin, dihydrocapsaicin, nordihydrocapsaicin, and homodihydrocapsaicin) which contribute to the pungency (Baruah *et al*., 2014; Reyes-Escogido *et al*., 2011) (Figure 1). Other capsaicinoids such as nonvamide and n-vanillyl decanamide are also present in significant levels. The total capsaicinoid content is in the range of 58.8% to 84.5% in acetone and hexane extracts of the fruits (Wesolowska *et al*., 2011). The capsaicin [8-methyl-N-vaniloid-6-nonenamide] and dihydrocapsaicin [N-(4-hydroxy-3-methoxybenzyl)-8-methylnonenamide] (Surh, 2002), present at levels of 37% and 29% of the total capsaicinoids respectively (Wesolowska *et al*., 2011), provide 90% of the pungency of chili pepper (Giuffrida *et al*., 2013).

Within the genus *Capsicum*, *C. chinense* contains the highest level of capsaicin (Bosland and Baral, 2007). The contents of tannins, flavonoids, saponins, terpenoids and carotenoids are higher in *C. annuum* than those of other species but *C. frutescence* contains the highest levels of flavonoids (Rahim and Mat, 2012) and anthraquinone (Emmanuel-Ikpeme *et al*., 2014) compared to the other domesticated species. Although the mean vitamin E content in chili pepper ranges from 1.98% to 2.10% (Wesolowska *et al*., 2011), the species *C. annuum* contains a higher vitamin E content than *C. frutescence* (Emmanuel-Ikpeme *et al*., 2014). The well-known chili pepper cultivar, bell pepper contains 20.73 g of dietary-fiber and 133 mg of vitamin C per 100 g of fresh fruit weight (Durucasu and Tokusoglu, 2007). It has been revealed that *C. annuum* would be a good source of Zn which is an essential micronutrient (Emmanuel-Ikpeme *et al*., 2014).

Effects of drying and ripening on phytochemicals

Conventional sun drying retains capsaicin in the chili pepper fruits (Magied *et al*., 2014), and it has been confirmed that drying under low temperature assures the high quality of chili pepper by preserving the phenolic compounds and vitamin C in the fruits (Moraes *et al*., 2013). Generally chili pepper has a higher amount of vitamin C (ascorbic acid) than many other vegetables showing its significant nutritional value (Kumar and Tata, 2009). It is also interesting to note that vitamin C is preserved during drying. The total phenolic and carotenoid contents increase during ripening, where the total phenolic content is doubled and the carotenoid content is increased by 10-fold. Although the total flavonoid content increases during initial ripening (i.e. yellowing), it is later reduced as fruits turn red (i.e. at complete ripening) (Shaha *et al*., 2013). The content of ascorbic acid is increased during drying of green chili peppers, while total phenolic content is decreased, resulting in lowered overall antioxidant capacity (Ozgur *et al*., 2011). However, Wangcharoen and Morasuk, (2008) reported that when chili pepper was dried at a temperature more than 100 °C, higher amounts of phenolic compounds were retained and hence resulting an increased antioxidant activity. It is also interesting to note that the antioxidant activity of dried chili pepper was maintained for as long as 18 months after harvesting (Ogiso *et al*., 2008).

ANTIOXIDANT ACTIVITY

The phytochemicals present in chili pepper possess anticancer properties (Chung *et al*., 2005), among them, vitamin C and phenolic compounds can act as antioxidants to counteract effects of reactive oxygen species (ROS) (Podsedek, 2007). ROS, which are generated from cellular metabolic processes, have been associated with several diseases such as cancer, diabetes, cardiovascular and neurological disorders (Sun-Hwa *et al*., 2007). Detoxification of ROS can be done by several enzymes present in the body as well as antioxidants obtained through dietary components (Halliwell, 2006) such as chili pepper.The antioxidant activity of chili pepper (Rosa *et al*., 2002) is only second to spinach among commonly consumed fruits and vegetables (Pellegrini *et al*., 2003). The antioxidant activity of chili pepper has been measured and studied using several assaying systems such as DPPH (2,2-diphenyl-1-picrylhydrazyl assay), ABTS (2,2'-azino-bis[3-ethylbenzothiazoline-6-sulphonic acid] assay), DMPD (Dimethyl-4-phenylenediamine assay),CuPRAC (Cupric reducing antioxidant capacity assay) and FRAP (Ferric ion reducing antioxidant power assay) (Krishna *et al*., 2010). Chili pepper contains both phenolic and

anthocyanin compounds which possess antioxidant activity (Borovsky *et al*., 2004; Howard *et al*., 2000; Marín *et al*., 2004; Mennen *et al*., 2005). Dietary phenolic compounds are advantageous as they donate H atoms to free radicals generated inside the body and neutralize them (Borovsky *et al*., 2004). The vitamins C and E present in chili pepper are also effective antioxidants (Sun-Hwa *et al*., 2007). Chili pepper is consumed in both dried and fresh forms, potentially influencing antioxidant levels, although studies have provided conflicting results regarding the effect of drying (Wangcharoen and Morasuk, 2008).

There are also differences for antioxidant capacity among different species and cultivars of chili pepper. Assessment of the antioxidant activity in Turkish pepper cultivars revealed an approximately 7-fold range in antioxidant activity (2.57 to 18.96 mmol of trolox per kg) (Frary *et al*., 2008). Out of the five chili pepper types tested, Bell and Caribe (a type of yellow fruited chili pepper) were reported to contain the highest antioxidant activity. The correlation between the phenolic content and the antioxidant activity was estimated as 91.4% (Medina-Juarez *et al*., 2012) indicating that majority of the antioxidant activity in chili pepper is due to the phenolic compounds. The highest level of phenolic content and the highest antioxidant activity compared to other species and cultivars were detected in bell pepper by Rahim and Mat, (2012), which was verified by Nadeem *et al*., (2011). *C. chinense* is also reported to contain higher levels of antioxidants such as carotenoids, ascorbate and glutathione and the concentration of glutathione is increased during ripening (Castro-Concha *et al*., 2012). Glutathione and ascorbate are the major antioxidants which contribute to Halliwell Asada Cycle, where detoxification of H_2O_2 produced in chloroplast takes place without the involvement of enzyme catalase (Foyer and Noctor, 2009).

ANTICANCER ACTIVITY

Application of *C. chinense* fruit extracts to the HepG2 cell lines (derived from a hepatocellular carcinoma) demonstrated the inhibition of cancer cell proliferation. This inhibitory activity was independently verified by using methylthiazol tetrazolium (MTT), lactate dehydrogenase leakage and nitrous oxide (NO) production assays (Amruthraj *et al*., 2014). The phytochemicals present in chili pepper trigger apoptosis of malignant cells. Capsaicin elicits the apoptosis pathway by repressing the plasma membrane NADH oxidoreductase enzyme in mitochondria (Morre *et al*., 1995, 1996). Capsaicin also binds with the ATP generating coenzyme Q, inhibiting its activity and destabilizing the electron flow in the mitochondria, thus producing ROS and triggering apoptosis (Macho *et al*., 1998, 1999, 2000; Wolvetang *et al*., 1996). The ROS have been shown to disrupt the mitochondrial membrane and induce apoptosis pathways in pancreatic cancer cells (Zhang *et al*., 2008). Capsaicin triggered the apoptosis pathway in human KB cancer cells (derived from *HeLa* cell line) by agitating the membrane potential of mitochondria and subsequently activating the caspase signaling pathway (Lin *et al*., 2013). However, capsaicin could also inhibit NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway which can cause apoptosis and minimize carcinogenic effects (Han *et al*., 2001; Patel *et al*., 2002). The studies on human cell cultures with exogenous capsaicin exhibited apoptosis (Ghosh and Basu, 2010), autophagy (Choi *et al*., 2009; Oh *et al*., 2010) and inhibition of cell metabolism (Arora *et al*., 2011). The carotenoid pigments present in bell pepper such as capsanthin, capsorubin and cryptocapsin possess high free radical scavenging activity (Matsufuji *et al*., 1998).

The experiments conducted using derived human cutaneous squamous cell carcinoma (SCC cell lines) concluded that capsaicin has prophylactic and therapeutic potentials to the skin cancers through the induction of apoptosis (Hail and Lotan, 2002) and modulating the epidermal growth factor receptor (EGFR) (Hwang *et al*., 2010). Capsaicin also down-regulates the expression of *Bcl-2* (B-cell lymphoma 2) (Jun *et al*., 2007), and thereby induces the apoptosis in B16-F10 melanoma cells (derived from *Mus musculus* skin melanoma). Chemically induced skin cancers in mouse models were also shown to be repressed by capsaicin (Park and Surh, 1997).

Capsaicin is identified as a blocker for the interleukin-6 induced transcription factor STAT3 [signal transducer and activator of transcription 3 (acute-phase response factor)] (Yu *et al*., 2009) which promotes tumor regenerative pathways. Thus, capsaicin could be used as a preventive and treatment drug for myeloma and other

cancers (Bhutani *et al*., 2007). *In vitro* studies using T-cell leukemia cell cultures have reported that capsaicin inhibits the growth of leukemia cells by degrading the TAX protein (human T-cell leukemia virus type 1 transcriptional transactivator) and increasing the NF-kB inhibitor alpha (Iκ-Bα) which arrests the cell cycle and triggers apoptosis. This demonstrates the possibility of using capsaicin as a chemo-preventive drug for leukemia (Zhang *et al*., 2003). Capsaicin is also known to induce the apoptosis pathway in leukemia cells through oxidative stress (Ito *et al*., 2004).

In glioma cancers of brain, capsaicin binds to the transient receptor potential vanilloid type I (TRPV I) receptor in glioma cells and induces apoptosis (Amantini *et al*., 2007). Gil and Kang, (2008) have also reported that capsaicin induces apoptosis in human glioma cells by down-regulating *Bcl-2* expression. Capsaicin is also known to possess inhibitory effects against the numerous cancers in the digestive system. Capsaicin possesses anti carcinogenic activity against tongue cancers (Tanaka *et al*., 2002) by inducing apoptosis through the stimulation of the expression of caspase-3 and caspase-9 activities (Ip *et al*., 2012a). Wu *et al*., (2006) reported that capsaicin triggers apoptosis via activating caspase-3 and generating the ROS in CE 81T/VGH cells (derived from esophagus epidermoid carcinoma). It has also been reported that capsaicin heightened the expression of proto-oncogenes (such as *c-myc and c-Ha-ras*), which trigger the apoptosis pathway, and tumor suppressor gene *p53* in SNU-1 cell line (derived from human stomach cancer cell) (Kim *et al*., 1997). Jung *et al*., (2001) reported that capsaicin induces apoptosis by activating the caspase-3 and down-regulating the *Bcl-2* in hepatocarcinoma cells SK-Hep-1 human liver cell line (derived from the ascetic fluid of a patient with adenocarcinoma). In pancreatic cancer cells, capsaicin also mediates ROS resulted mitochondrial damages and induces apoptosis.In colorectal cancer cells capsaicin is known to suppress the β-catenin dependent signaling pathway. Capsaicin restricts the expression of transcription factor 4 (TCF-4) and inhibits the interaction between β-catenin and TCF-4 suggesting the potential use of chili pepper as a treatment for colorectal cancers (Lee *et al*., 2012). Lee *et al*., (2010) also reported that capsaicin represses the cell proliferation in colorectal cancer cell lines.

The anticancer role of capsaicin is also observed in lung associated carcinoma. Capsaicin stabilizes the mitochondrial related enzymes in lungs which minimize the cancer risk induced by using benzopyrene in mouse models (Anandakumar *et al*., 2007). Jang *et al*., (1989) have reported that capsaicin reduces the risk of lung tumor development induced by polycyclic aromatic hydrocarbons. According to Brown *et al*., (2010) capsaicin can be used to treat human small cell lung cancer since it has anti-proliferative activity in both cell culture experiments and mouse models by inhibiting the *E2F* (a family of transcription factor genesin higher eukaryotes) responses and proliferative gene expression which triggers the anti-proliferative activity. The apoptosis inducing mechanisms in NPC cell lines (derived from human nasopharyngeal carcinoma) are reported in Ip *et al*., (2012b) and it was found that capsaicin induces endoplasmic reticulum stress, caspase-3 activation and mitochondrial depolarization. In addition capsaicin has an inhibitory activity against the development of prostate cancer by down-regulating the expression of prostate specific antigen (PSA) (Mori *et al*., 2006). The reported inhibitory effects of the capsaicinoids on diverse cancer cell lines are summarized in Table 1.

Table 1: The inhibitory effects of capsaicinoids on diverse cell lines mimicking the anticancer activity.

Cancer	Cell line	Effect/s	Reference
Leukemia	HPB-ATL-T (adult T-cell leukemia)	Inhibit growth.	Zhang *et al.*, (2003)
	NB4 –PL (neuroblastoma promyelocytic leukemia) and Kasumi-1 (myeloid leukemia)	Induce apoptosis by oxidative stress.	Ito *et al*., (2004)
	HL-60 (human myelocytic leukemia)	Induce apoptosis by caspase-3-dependent mechanism.	Tsou *et al*., (2006)
Multiple myeloma	U266 (human multiple myeloma) and MM.1S (immunoglobulin A lambda myeloma)	Inhibit the tumorigenesis by blocking STAT3 [signal transducer and activator of transcription 3 (acute-phase response factor)].	Bhutani *et al*., (2007)
Cutaneous cell carcinoma	SRB-12 (scavenger receptor class B type 12 derived from an epidermal lesion of a patient) and COLO 16 (squamous-cell carcinoma)	Arrest cell cycle at G1 stage and induce apoptosis by mitochondrial depolarization.	Hail and Lotan, (2002)
Glioma	A172 (human glioblastoma)	Induce apoptosis by generating ROS.	Lee *et al*., (2000)
	FLS (fibroblast-like synoviocyte) and FC1 (glioblastoma)	Induce apoptosis by mitochondrial depolarization.	Amantini *et al*., (2007)
Tongue cancer	SCC-4 (squamous-cell carcinoma) human tongue cancer cells	Induce apoptosis by mitochondria dependent and independent mechanisms	Ip *et al*., (2012a)
Nasopharyngeal carcinoma	NPC-TW 039 (human nasopharyngeal carcinoma)	Induce apoptosis by endoplasmic reticulum stress and mitochondrial depolarization.	Ip *et al*., (2012b)
Esophageal carcinoma	CE 81T/VGH (human esophagus epidermoid carcinoma)	Arrest cell cycle at G0-G1 phase.	Wu *et al*., (2006)
Gastric cancer	SNU-1. NIH/3T3 (a Korean stomach cancer)	Alter the expression of tumor forming genes and induce the apoptosis.	Kim *et al*., (1997)
Pancreatic cancer	AsPC-1 and BxPC-3 (human pancreatic cancer)	Induce apoptosis by generating ROS.	Zhang *et al*., (2008)
		Induce apoptosis by oxidative stress and mitochondrial damage.	Pramanik *et al*., (2011)
Hepato carcinoma	SK-Hep-1 (sloan kettering hepatocarcinoma)	Induce apoptosis by caspase-3-dependent mechanism.	Jung *et al*., (2001)
	HepG2 (human hepatoma)	Induce apoptosis by ROS disruption.	Huang *et al*., (2009)
Colon carcinoma	HT-29 (human colon cancer)	Induce apoptosis by activating the peroxisome proliferator-activated receptor gamma.	Kim *et al*., (2004)
	Colo 205 (human colon cancer)	Induce apoptosis by caspase-8 dependent mechanism.	Lu *et al*., (2010)
Lung cancer	NCI-H69, NCI-H82 (small cell lung cancer)	Arrest cell cycle at G1.	Brown *et al*., (2010)
Breast cancer	MCF-7 (Michigan Cancer Foundation-7) (human breast cancer)	Induce apoptosis by caspase-independent pathway.	Chou *et al*., (2009)
	MCF-7 (Michigan Cancer Foundation-7), T47D, BT-474, SKBR-3 and MDA-MB231 (breast cancer)	Arrest cell cycle and induce apoptosis by altering the EGFR/HER-2 pathway.	Thoennissen *et al*., (2010)
Prostate cancer	LNCaP (lymph node carcinoma of the prostate), PC-3 and DU-145 (prostate cancer)	Confer anti- proliferative activity by downregulating PSA.	Mori *et al*., (2006)
	PC-3 (prostate cancer)	Induce apoptosis by ROS generation.	Sanchez *et al*., (2007)
Human KB carcinoma	KB (derived from HeLa cell line)	Arrest cell cycle at G2/M phase and induce apoptosis.	Lin *et al*., (2013)

ANTI-INFLAMMATORY AND PAIN RELIEVING ACTIVITIES

Chili pepper extracts contain anti-inflammatory (Kim *et al*., 2003; Lee *et al*., 2005) and anti-allergic properties (Lee *et al*., 2005). Out of the numerous phytochemicals in chili pepper, capsaicin is reported mainly to confer the anti-inflammatory activity (Kim *et al*., 2003) but the colour pigment anthocyanin has also been reported to possess significant anti-inflammatory activity (Wang *et al*., 1999). Capsaicin overwhelmed the obesity induced inflammatory responses from macrophages in adipose tissue (Kang *et al*., 2007) indicating the potential applications as an analgesic. Inhibition of the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β) by capsaicin reduces the inflammatory responses induced by antigens (Spiller *et al*., 2008). It was also found that anti-inflammatory activity was not triggered by vanilloid receptor-1 but by inhibiting the IkB-a, which degrades the lipopolysaccharide stimulated peritoneal macrophages (Kim *et al*., 2003). Capsaicin and nordihydrocapsiate (a type of capsinoid) inhibit the early T cell activation events such as NF-κB activation (Sancho *et al*., 2002). Capsaicin can be used to treat rheumatoid arthritis, osteoarthritis and peripheral arthritis (Cordell and Araujo, 1993) as it reduces the inflammatory heat. It can be used to relieve the pain from noxious chemical hyperalgesia as well (Arora *et al*., 2011; Fraenkel *et al*., 2004) because it has an ability to control the secretion of neurotransmitter relating to the pain (Lynn, 1990). The analgesic activity of capsaicin can be used to minimize neuropathic pain conditions (Sindrup and Jensen, 1999). When recovering from cancer treatments, capsaicin can be used as a temporary pain relieving agent for oral mucositis which results from chemo and radiation therapies (Berger *et al*., 1995). Cruz, (2004) reported that capsaicin can reduce the bladder pain associated with patients who have hypersensitive disorders.

ANTIDIABETIC/ANTIHYPERGLYCEMIC ACTIVITIES

It is estimated that by 2025, the number of diabetic patients in the world could go up to 300 million (Sy *et al*., 2005) and therefore more efficient and economical treatments are needed. Chili pepper, with a significant potential as a candidate plant for new drugs, has shown to possess promising antidiabetic activity (Okumura *et al*., 2012) as it contains inhibitors for α-amylase and α-glucosidase which are required for the degradation of polysaccharides and disaccharides. Chili pepper is also reported to lower the absorption of D-glucose in the intestine, thus it can be used to control carbohydrate digestion and post-prandial glucose level rise (Kwon *et al*., 2007) (reviewed in Adefegha and Oboh, 2013). The effect of capsaicin on carbohydrate metabolism in exercising and resting states were determined using human subjects and it was found that capsaicin increases the plasma epinephrine and norepinephrine by increasing O_2 consumption. This implies an increase of carbohydrate oxidation due to capsaicin (Lim *et al*., 1997). Domotor *et al*., (2006) further confirmed using human subjects, that capsaicin increases the glucose adsorption and increases the level of blood glucagon concentration. The obesity induced insulin resistance which is a metabolic disorder that can be minimized by using capsaicin reducing the risk of having type-2 diabetes in the future. Capsaicin alters the gene expression, lessens the glucose intolerance (hyperglycemia) and reduces the fasting glucose levels in mouse models (Kang *et al*., 2010). Capsaicin is known to increase the rate of carbohydrate metabolism in human subjects and in addition, the rat models were used to gain a deep insight on the antidiabetic effects of chili pepper. Administration of chili pepper to rats reduces blood glucose levels (Magied *et al*., 2014; Okumura *et al*., 2012) through the induction of thermogenesis reactions such as lipid and glucose metabolism leading to the lowering of fatty acid storage in the body. Induction of thermogenesis reactions are achieved by activating the sympathetic nervous system which promotes thermogenesis reactions (Okumura *et al*., 2012). *C. frutescence* is always a center of attraction in this regard as it was shown to increase the blood insulin level in type-2 diabetes of rats (Islam and Choi, 2008). Furthermore *C. frutescence* was found to increase the affinity of insulin towards its receptor (glucose) implying the potential of using chili pepper as a treatment for diabetes (Anthony *et al*., 2013; Patel *et al*., 2012).

ANTICHOLESTEREMIC ACTIVITY AND THE EFFECTS ON LIPID METABOLISM

Chili pepper is reported to possess hypocholesteremic and hypolipidemic activities, thus it can be used to treat and prevent cardiovascular diseases (Kempaiah and Srinivasan, 2002; Srinivasan *et al*., 2004). Capsaicin can induce the thermogenesis and lipid metabolism pathways (Ahuja *et al*., 2006) by inhibiting the fatty acid storage in the body (Okumura *et al*., 2012; Yoshioka *et al*., 1998) showing its potential to use as a treatment to control obesity. Capsaicin stimulates catecholamine secretion leading to the release of β3 adrenergic stimulation which generates thermogenesis reaction (Kawada *et al*., 1986; Jimenez *et al*., 2002; Watanabe *et al*., 1987). Capsaicin specifically alters the lipid metabolism by lipid oxidation of the high fat diets in the gastrointestinal tract. Kempaiah *et al*., (2005) reported that capsaicin inhibits low density lipoprotein oxidation induced by copper (*in vitro*) and ferrous (*in vivo*) ions. Ahuja *et al*., (2006) reported that capsaicin and dihydrocapsaicin inhibit the copper-induced serum lipoprotein oxidation. Capsaicin has proven protective effects on hepatic lipid peroxidation in rats (Kempaiah *et al*., 2005). Another study on rats revealed that administering chili pepper along with high fat diet affects HDL and LDL cholesterol, total glyceroids and total lipid contents, and thereby reduces serum cholesterols significantly compared to that of control treatments (Magied *et al*., 2014). Similarly, the serum lipoprotein content was reported to be reduced in human subjects who had daily chili pepper diets (Ahuja and Ball, 2006). Chili pepper can be used to control lipid oxidation since it possesses higher antioxidant activity than most of the other vegetables (Embuscado, 2015). Experiments with human subjects also have shown that dietary capsaicin induces abdominal fat loss by increasing fat oxidation (Snitker *et al*., 2009). Further studies with human subjects with higher Body Mass Index (BMI) demonstrated that consumption of capsaicinoids increased fat oxidation rate and energy expenditure in the body, suggesting it may be valuable to facilitate reduction in BMI (Inoue *et al*., 2007).

ANTICLOTTING EFFECT

The phytochemicals present in chili pepper have proven healing effects on cardiovascular diseases in rodents (Ogunlade *et al*., 2012). Experiments conducted using rat models suggested that chili pepper can reduce the risk of cardiovascular diseases and arthritis (Kritchevsky, 1992). Capsaicin was shown to inhibit platelet aggregation (Adams, 2009; Hogaboam and Wallace, 1991) by stabilizing the membranes of red blood cells via interfering with the enzyme phospholipase A2 (PLA2) (Wang *et al*., 1984). Mouse model studies revealed that capsaicin, which inhibits platelet formation by inhibiting the clotting factors VIII: C and IX (Adams *et al*., 2009), is more effective than aspirin in averting the acute pulmonary thromboembolism (Wang *et al*., 1985). Therefore, capsaicin may have the potential to be developed as a therapeutic and preventive agent of cardiovascular diseases.

ANTIMICROBIAL ACTIVITY

Herbal materials have long been appreciated because of their proven antimicrobial effects (Alavijeh *et al*., 2012). In addition to the use of chili pepper as a spice, it has been widely used as an agent to preserve food (Omolo *et al*., 2014). The antimicrobial activity of the compounds present in *Capsicum* species were reported in many studies (Careaga *et al*., 2003; Cichewicz and Thorpe, 1996; Omolo *et al*., 2014). In addition to the pungency related phytochemicals, the pigment anthocyanin in chili pepper also possesses antimicrobial activity (Zhao *et al*., 2009). The antibacterial activities of chili pepper were reported against the noxious pathogens *Bacillus cereus*, *B. subtilis*, *Clostridium sporogenes*, *C. tetani*, *Streptococcus pyogenes* (Cichewicz and Thorpe, 1996), *Staphylococcus aureus* (Molina-Torres *et al*., 1999), *Escherichia coli*, *Pseudomonas aeruginosa*, *Sarcina lutea*, *Candida albicans* (Soetarno *et al*., 1997) and *Vibrio cholera* (Chatterjee *et al*., 2010). The bactericidal activity of capsaicin against the gastric pathogen *Helicobacter pyroli* was evaluated and the minimum inhibitory concentration (MIC) was found to be 10 µg/ml (Jones *et al*., 1997) and confirmed by Zeyrek and Oguz, (2005). Similarly MIC values of 25 µg/ml against *B. subtilis*, 200-300 µg/ml against *E. coli* (Molina-Torres *et al*., 1999), 15 µl/g against *Salmonella typhimurium* and5-15 µl/g against *P. aeruginosa* (Careaga *et al*., 2003) were reported. Capsaicin also possesses inhibitory activity against numerous antibiotic resistant microbial strains (Zeyrek *and* Oguz, 2005). The acetonitrile extracts of phytochemicals chrysoeriol,

dihydrocapsaicin and capsaicin from *C. frutescence* were found to have antimicrobial activity against *Enterococcus faecalis*, *B. subtillis*, *S. aureus*, *P. aeruginosa*, *Klebsiella pneumoniae*, *E. coli* and *C. albicans* (Nascimento *et al.*, 2014). The mechanism of antimicrobial activity of capsaicin was evaluated through DNA microarray technology and it was found that capsaicin has a toxic effect against yeast cells and induces their pleiotrophic drug resistance network which expresses genes related to osmotic stress and membrane biosynthesis (Kurita *et al*., 2002).

OTHER MISCELLANEOUS MEDICINAL VALUES

It has long been believed that chili pepper promotes proper functioning and good health of digestive tract. Capsaicin stimulates the secretion of saliva and gastric juice which is vital for efficient digestion of food and to overcome gastrointestinal abnormalities (Bosland, 1996). Capsaicin also increases the gastric blood flow by inducing the gastric sub mucosal arteriolar dilation (Chen *et al*., 1992) which is important for efficient food absorption. Zeyrek and Oguz, (2005) reported that capsaicin inhibits the growth of *H. pylori*, hence chili pepper may have value as a treatment for ulcers in the stomach and duodenum. Chili pepper exhibited gastric ulcer protective activity (Das *et al*., 2008) and capsaicin provided hepato-protective activity as it promoted recovery from CCl_4 induced liver injuries in rat (Hassan *et al*., 2012). Finally, ripe red chili pepper has shown inhibitory activity against the angiotensin-1 converting enzyme which increases blood pressure, suggesting that chili pepper has anti-hypertension activity (Ranilla *et al*., 2010).

CONCLUSION

The phytochemicals present in chili pepper such as capsaicin have the potential to provide numerous medicinal benefits. It is clear that, ethno-medicinal applications reported in the historical records are supported by the latest findings on the medicinal properties of chili pepper. The anticancer activity is conferred through the inhibition of cancer proliferation, induction of apoptosis and detention of cell cycle. These activities were confirmed using animal models and human cancer cell lines. In addition, analgesic, antihyperglycemic, antibacterial and antifungal effects of chili pepper were also reported. The healing effects of chili pepper on other disease conditions such as strokes, hypercholesterolemia, aging, obesity, and ulcers associated with the digestive tract were well studied. The underlying phytochemicals and their associated molecular pathways have been characterized to show the mechanisms of action. The inter-genera diversity of the medicinal properties have been studied though mainly limited to the fruits of two main species, *C. annuum* and *C. frutescen*e and, the famous cultivar bell pepper which is also a *C. annuum*. Further studies are essential to explore and characterize more efficient bio-active compounds from the underutilized *Capsicum* spp. in diverse geographical locations. The wealth of information that is currently available regarding the medicinal properties of chili pepper can be used to develop novel drugs to combat cancers and other important ailments mentioned.

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