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Potential Phytopharmacy and Food Applications of *Capsicum* spp.: A Comprehensive Review

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Capsicum genus (Solanaceae) is native to the Americas. Today, it is an important agricultural crop cultivated around the world, not only due to its economic importance, but also for the nutritional value of the fruits. Among their phytochemical constituents, capsaicinoids are characteristic and responsible of the pungency of sharp-tasting cultivars. Moreover, *Capsicum* and capsaicinoids (mainly, capsaicin) have been largely studied because of their health benefits. Thus, this study reviews the scientific knowledge about *Capsicum* spp. and their phytochemicals against cancer, diabetes, gastrointestinal diseases, pain, and metabolic syndrome, as well as their antioxidant and antimicrobial activity. These bioactivities can be the basis of the formulation of functional ingredients and natural preservatives containing *Capsicum* extracts or isolated compounds.

Keywords: *Capsicum*, Capsaicin, Pepper, Metabolic syndrome, Natural preservative.

Introduction

Medicinal plants are considered as significant natural remedies for the treatment of various diseases [1-7]. Natural products of higher plants be potential provide a new source of curative agents with maybe novel mechanisms of activity [8-11].

Capsicum spp. are popular vegetables grown and consumed throughout the world [12]. They belong to the family Solanaceae that comprises 90 genera and 2000 species. This plant family is native to the Americas, and includes vegetables such as pepper, tomato, and potato [13]. In fact, chili peppers (also chile pepper, chilli pepper, or simply chilli) are the oldest crops cultivated by Native Americans between 5200 and 3400 BC [14]. Moreover, *Capsicum* spp. have been used in traditional medicinal practices since pre-Hispanic times from Aztecs and Mayans. Today, this genus is cultivated in various regions of the world including tropical, subtropical and temperate regions of Africa, Asia, and America, as well as the Mediterranean basin, thanks to its economic importance, and the nutritional value of the fruits (Table 1). Among the five recognized cultivated species of this genus are: *C. chinense, C. annuum*, *C. pubescens*, *C. baccatum*, and *C. frutescens* [15, 16]. Peppers are a good source of vitamins C and E, provitamin A, carotenoids, as well as phenolic compounds; all these components are related to the total antioxidant activity of this plant food, and its bioactive properties [13]. The most characteristic phenolic derivatives found in pepper fruits is capsaicinoids (vanillylamine linked with a branched-chain fatty acid), such as capsaicin and dihydrocapsaicin (Figure 1), which are responsible for 90% of the pungency of peppers [17]. The degree of pungency depends on the *Capsicum* species and cultivar. The contents of these compounds may vary between undetectable in certain non-pungent cultivars to 664 mg/100 g, in pungent ones, respectively [18]. The capsinoids capsiate and dihydrocapsiate, two non-pungent analogues of capsaicin and dihydrocapsaicin respectively, have also been described in *Capsicum* spp. [19]. Other phenolic compounds are flavonols and flavone glycosides as well as hydroxycinnamic acids [13].

Some of the health benefits related to *Capsicum* ssp. consumption as part of a normal diet or related to its bioactive metabolites are shown in Figure 1. These bioactivities are reviewed here in the subsequent sections.

Table 1: Nutritional composition of *Capsicum* spp. fruit (per 100 g of edible portion) [20].

Nutrient[a]	Spices, pepper, red or cayenne[b]	Peppers, sweet, green, raw[c]	Peppers, hot chili, green, raw[d]	Peppers, sweet, yellow, raw[c]
Water (g)	8.05	93.89	87.74	92.02
Protein (g)	12.01	0.86	2.00	1.00
Energy (kcal)	318	20	40	27
Carbohydrate (g)	56.63	4.64	9.46	6.32
Calcium (mg)	148	10	18	11
Phosphorus (mg)	293	20	46	24
Selenium (µg)	8.8	0.0	0.5	0.3
Iron (mg)	7.80	0.34	1.20	4
Sodium (mg)	30	3	7	2
Copper (mg)	0.373	0.066	0.30	0.107
Potassium (mg)	2014	175	340	212
Fatty acids, total saturated (g)	3.260	0.058	0.021	0.031
Fatty acids, total monounsaturated (g)	2.750	0.008	0.011	
Total lipids (fat) (g)	17.27	0.17	0.20	0.21
Ash (g)	6.04	0.43	0.60	0.45
Niacin (mg)	8.701	0.480	0.950	0.890
Vitamin C, total ascorbic (mg)	76.4	80.4	242.5	183.5
Thiamin (mg)	0.328	0.047	0.090	0.028
Vitamin B-6 (mg)	2.450	0.224	0.278	0.168
Carotene, beta (mg)	21.84	0.208	0.671	0.120
Cryptoxanthin, beta (mg)	6.252	0.007	0.050	

[a]Composition data obtained from the National Nutrient Database for Standard Reference Release 28, USDA Food Composition database (https://ndb.nal.usda.gov/ndb/; accesed 18/11/2017);
[b]Scientific name: *Capsicum frutescens* or *Capsicum annuum.*
[c]Scientific name: *Capsicum annuum.*
[d]Scientific name: *Capsicum frutescens.*

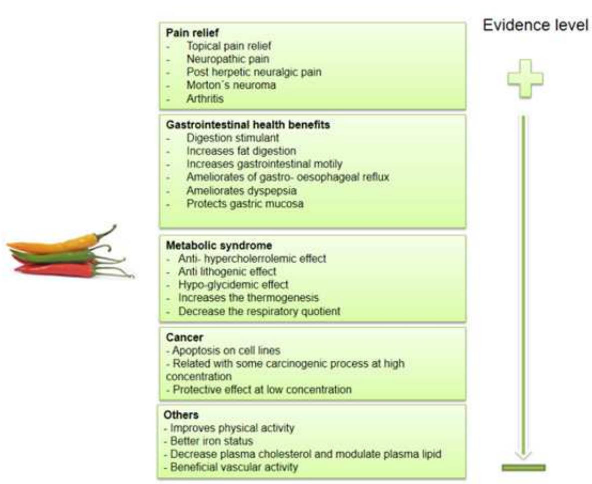

Figure 1. Example of health benefits of the consumption of *Capsicum* spp

Capsaicin is the most studied bioactive compound of *Capsicum*. It is considered safe in a normal daily intake. Its lethal dose (LD_{50}) estimated in humans is between 0.5–5 g capsaicin/kg (around 50,000 mg per person) [21]. However, it is known that capsaicin present in hot varieties can cause skin irritation and edema. Also, it can produce eye irritation and cause corneal lesions in rats and mice. Inhalation causes bronchoconstriction, coughing, nausea, and loss of coordination in the upper body. Exposure to capsaicinoids may result in temporary blindness, lacrimation, burning sensation, pain and skin redness, nasal irritation as well as dyspnea. These effects can be avoided using non-pungent peppers.

Cultivation of *Capsicum* species

Capsicum is a cool season crop, but *Capsicum* can be grown throughout the year under controlled temperature and moisture conditions. The average day temperature requirement is 25-30°C and night temperature 18-20°C with relative humidity of 50- 60%. This crop is temperature sensitive if the temperature rises above 35ºC or falls below 12ºC, it will have adverse effects [22, 23]. The yield of green capsicum depends upon variety and season, generally it yields 20-40 tons per hectare in about 4-5 months, whereas in green house this yield is 80-100 tons per hectare but the duration of crop is 7-10 months [12]. For good production it is very important that the soil is properly plowed to provide a fine tilth. Raised beds of size 90-100 cm wide and 15-22 cm height are formed. Moreover, organic manure at the rate of 20-25 kg/m^2 must be mixed with soil before cultivation. One application is sufficient to grow three capsicum crops successively [12].

Productivity of capsicum is affected by soil solarization, organic fertilizer and endomycorrhizae [24, 25]. Proper development of plants, flowers, and fruits can be achieved by adding organic fertilizer [26]. The addition of organic fertilizer not only reduced the cost of chemical fertilizer but also resulted in the production of superior quality fruit [27, 28]. The addition of organic fertilizer in capsicum field resulted in significant increase in soil carbon, nitrogen, pH, cation exchange capacity, and exchangeable Ca, Mg, and K which invariably enhance crop yield and productivity of pepper [29]. However, combination of sunlight and organic fertilizers has positive effect on crop productivity. The pH requirement is 6-7 for getting the high production. The yield of several crops is enhanced by vesicular arbuscular mycorrhizal fungi [30-32]. They are important in ecological agriculture because of the benefits they provide to the majority of cultivars and the conservation of the environment by acting as biofertilizers, biological protectors, and biological control agents [33] .

The most important issue in cultivation of *Capsicum* is the high susceptibility of the crop to a number of microorganisms, viruses and insects [34]. The common diseases of *Capsicum* are root rot, bacterial leaf spot, leaf curl, mosaic, seedling damping off and pests attacking fruits. The susceptibility of the plants varies with climate, location and time. Susceptibility of *Capsicum* and mosaic incidence reported from 70-90 %. However, leaf curl is reported to be the most devastating disease for *Capsicum*. The damage of crops due to pathogen attack can cause complete loss [35]. Hence, the areas with high rainfall and humidity are not suitable for its cultivation because they promote foliar diseases. Moreover the areas with high wind velocity are not suitable because they could enhance maintenance cost of the structure. The most recommended soil for capsicum is well drained sandy loam soil with good percolation [36].

Traditional methods are recommended to combat the sequential or simultaneous infectious diseases caused by microbes and pathogen treatment with chemicals starting with seed, soil and periodic spraying during growth, maturation and ripening [37, 38]. Identification of resistant varieties and breeding for disease-resistant varieties is in practice worldwide for *Capsicum* cultivation. The pure line progeny selection has been employed for genetic upgrading of economic attributes of *Capsicum* [35].

Phytochemical composition of *Capsicum* plants

Pepper (*C. annuum* L.) has been known to cure various degenerative human disorders due to the presence of bioactive compounds [39, 40]. Bell peppers (also known as sweet pepper or pepper) are a significant source of phenolic compounds such as quercetin, luteolin, and capsaicinoids [41-43]. These phenolic compounds provide protection against cancer insurgence, diabetes, oxidative stress, cardiovascular diseases, and neural disorders such as Parkinson's and Alzheimer's disease [39, 41, 44].

C. annuum can be consumed fresh or processed, as preserves, sauces, or dehydrated powder. It is an important source of nutrients, such as provitamin A (carotene), vitamin C (ascorbic acid), chlorophyll, carotenoids, tocopherols and calcium in the human diet [45, 46]. Capsaicinoids (Figure 2) are exhibits several applications in food and pharmacy. Additional capsaicinoids consist of dihydrocapsaicin, homodihydrocapsaicin, nordihydrocapsaicin, norcapsaicin, homocapsaicin, and nornorcapsaicin [47]. Capsaicinoids are compounds characteristic in pungent pepper, which is normally consumed in South America. Nevertheless, a recent study on three different non-pungent varieties, 'Italian Sweet' (green pepper), 'Lamuyo' (yellow pepper), and 'California wonder' (red pepper) showed that the main phenolic classes are glycoside derivatives of flavonoids, such as quercetin 3,7-di-*O*-α-L-rhamnopyranoside and narigenin-7-*O*-β-D-(3″-*p*-coumaroyl)-glucopyranoside [13] . Other compounds of non-pungent cultivars of *C. annuum* are capsiate, dihydrocapsiate, and nordihydrocapsiate [48] (Figure 2).

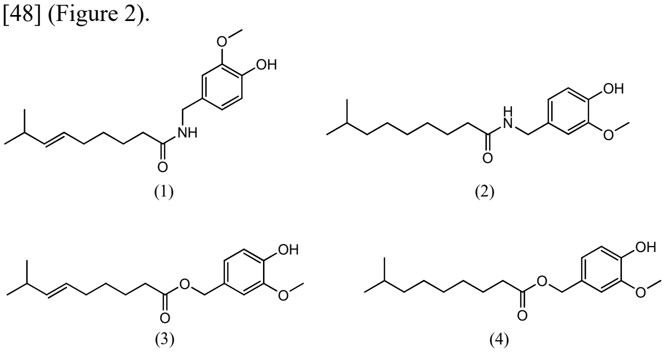

Figure 2. Examples of chemical structures of capsaicinoids and capsinoids: capsaicin (1), dihydrocapsaicin (2), capsiate (3), and dihydrocapsiate (4).

Bell pepper changes its color from green to yellow and red, while ripening. Chlorophyll and carotenoids are the major phytochemicals responsible for green color [49], while compounds such as α- and β-carotene, zeaxanthin, luteolin and β-cryptoxanthin are responsible for the yellow color in bell pepper [19]. The red color of bell pepper is mainly due to the presence of capsanthin, capsorubin and capsanthin-5,6-epoxide [50]. The concentrations of bioactive compounds in *C. annuum* is significantly affected by different maturity stages [49, 50].

There are different types of metabolites present in *C. annuum* such as four quercetin glycosides namely quercetin 3-*O*-rhamnoside-7-*O*-glucoside, quercetin 3-*O*-rhamnoside, and quercetin 3-*O*-glucoside-7-*O*-rhamnoside with rhamnoside-glucoside attached either at the *C*-3 or *C*-7 position. Furthermore, five luteolin *C*-glycosides, luteolin 8-*C*-hexoside, luteolin 6-*C*-hexoside, luteolin 6-*C*-hexoside-8-*C*-pentoside, luteolin 6-*C*-pentoside-8-*C*-hexoside, and luteolin 6,8-di-*C*-hexoside along with two luteolin *O*-glycosides, luteolin 7-*O*-(2-apiosyl)-glucoside, and luteolin (apiosyl-acetyl)-glucoside have also been identified in the pericarp of pepper fruits. In addition, two apigenin *C*-glycosides were also identified as apigenin 6-*C*-pentoside-8-*C*-hexoside and apigenin 6,8-di-*C*-hexoside [51]. Structures of *C*-glycosides isolated from pepper fruit (*C. annuum* L., var. Capel Hot) are luteolin 6-*C*-glucoside, luteolin 6,8-di-*C*-glucoside and apigenin 6-*C*-glucoside-8-*C*-arabinoside [52]. The composition of polyphenols mainly varied with genetics, developmental stage and environmental conditions [53].

Traditional medicinal use of *Capsicum* genus

Native from Mexico and Central America, *Capsicum* spp. have been used in traditional medicine practices since pre-Hispanic times from Aztecs and Mayans, which is well documented in several codices. The most important of them is considered *Libellus de Medicinabilus Indorum Herbtis* (Little book of the medicinal herbs of the Indians) written by the indigenous medicine man Martin de la Cruz in 1522 [54]. At the beginning of the 20th century, studies of the botanical pharmacopeia of the indigenous Mayan inhabitants of Mesoamerica reported approximately 32 different health-related uses of *Capsicum* spp. [55], including treatment for arthritis, rheumatism, stomach aches, skin rashes as well as for alleviating dog and snake bites. However, the use of *Capsicum* fruits is not exclusively from Latin America, and their medicinal uses have been spread worldwide along with their consumption and cultivation. Hence, *Capsicum* fruits are mentioned in a classic text of the Tibetan medical tradition, the "Blue Beryll" to increase the digestive warmth of the stomach and as medication for the alleviation of edema, hemorrhoids, parasitic protozoa, and leprosy [56]. Furthermore, in Africa they are considered as antispasmodic, pulmonary disinfectant, counter-irritant and antitussive agents [57]. In general, *Capsicum* fruits are applied topically in pain disorders, neuropathy, cluster headache, migraine, psoriasis, trigeminal neuralgia and herpes zoster. Also, it has been used to treat dyspepsia, loss of appetite, flatulence, atherosclerosis, stroke, heart disease, and muscle tension [58]. Today, the fruits, fresh or dried, are consumed daily by a quarter of the global population as spices, food supplements, and additives.

Food preservative applications of plants of the genus *Capsicum*

Today's consumers are focused on the types of ingredients that are used in foods for flavoring, coloring and preservation [59-65]. To avoid the stigma of complex chemical names, food companies are seeking alternatives to the use of complex preservatives. Consumers want "clean labels" and products that do not contain traditional chemical preservatives.

There is an increasing trend to use natural bioingredients in food for preservation, extension of shelf-life, and microbial safety [66-70]. Spices have found application in a wide range of foods due to the extensive array of phytochemicals they possess. Ginger, allspice, pepper, nutmeg, cloves, celery, leaves, chives, and pepper are just a few spices produced through the world. Capsaicin, the major chemical compound found in pungent peppers, is reported to have antimicrobial activity against Gram-negative and Gram-positive spoilage and pathogenic bacteria [71]. As indicated elsewhere in this review, capsaicin contributes to the pungency of peppers, which can limit application in certain food systems.

The antimicrobial activity of peppers was thought to be strictly associated with capsaicin and dihydrocapsaicin, although research suggests this may not be the case [72]. Antimicrobial activity of capsaicin, dihydrocapsaicin and chrysoeriol isolated from the acetonitrile extract of *C. frutescens* was tested against seven microorganisms: *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis, Bacillus subtilis, Staphylococcus aureus,* and *Candida albicans*. Surprisingly, under the conditions evaluated, chrysoeriol showed the greatest activity against all microorganisms evaluated with an MIC of ≤1 μg/mL [73]. In a further effort to address this issue, subfractions of crude jalapeño extract were collected and evaluated for antimicrobial activity against *Listeria monocytogenes*, *Salmonella enterica* Baildon, and *E. coli* O157:H7. Of the fractions collected they consistently inhibited growth of *L. monocytogenes*, had no effect on *E. coli* O157:H7 and only one fraction inhibited *Salmonella* [74].

The fractions that exhibited the greatest activity were matched to capsianosides, which are acyclic diterpene glycosides. These studies are not entirely contradictory and demonstrate that several compounds produced by *Capsicum* plants exhibit antimicrobial activity.

Rather than investigate the antimicrobial action of specific components, three habañero chili sauces were used directly in a well-dilution assay [75]. *E. coli, Bacillus thuringiensis, Yersinia enterocolitica*, and *Salmonella enterica* subsp. *typhimurium* were inoculated into wells containing chili sauce and Mueller-Hinton broth. At the highest concentration (1:3 dilution) of chili sauce, *Y. enterocolitica* and *S. enterica* were completely inhibited, while the growth of *E. coli* and *B. thuringiensis* was not influenced.

Research clearly suggests that various phytochemicals of peppers exhibit antimicrobial activity. The coupling of capsaicin, dihydrocapsaicin and chrysoeriol with antimicrobial compounds derived from other plants or microbiological sources may prove more effective and mitigate some negative aspects of *Capsicum* plant-derived compounds linked to pungency. Moreover, novel methods of food processing, including high pressure processing (HPP), pulsed light, and UV-light, are becoming more common to control pathogens. Utilization of *Capsicum* derived compounds with processing methods that do not influence organoleptic qualities of a food must be considered. Examples of this type of hurdle technology processing are rich in literature, but using other type of natural products. As an example, the compound nisin was used in combination with HPP to control the thermoacidophilic and spore-forming bacterium, *Alicyclobacillus acidoterrestris*, in apple juice [76]. The investigators demonstrated that using pressure of 200 MPa for 45 min with a nisin concentration of 250 IU/mL enabled total spore inactivation (over 6 log). Although the time requirement of the process would be prohibitive for commercial use, the study demonstrates the proof-of-concept.

A major global concern is the prevalence of antibiotic resistant foodborne pathogens. Some consumers are concerned that the use of food preservatives, sanitizers and others types of antimicrobials by the food industry contributes to the development of antibiotic resistant bacteria. Researchers investigated the synergistic effect of capsaicin and ciprofloxacin on *S. aureus* [77] showing that the MIC of ciprofloxacin was reduced 2 to 4 fold in the presence of capsaicin.

The antimicrobial action of *Capsicum* phytochemicals is typically evaluated under *in vitro* conditions. However, these studies may not translate to activity in a complex food matrix. Thus, research investigated the inhibitory effect of extracts from *Capsicum* against *S. typhimurium* and *P. aeruginosa* inoculated in minced beef. A concentration of ml/100 g of meat showed a bactericidal effect for *P. aeruginosa*, whereas mL/100g of meat inactivated *Salmonella*. Interestingly, combining the *Capsicum* extract with sodium chloride (1%, w/w) was only beneficial against *P. aeruginosa* [78]. The antimicrobial characteristics of sweet and hot pepper extracts were evaluated for controlling spoilage and pathogenic bacteria associated with Fassiekh (wet-salted fermented fish) products. The research demonstrates that extracts from hot pepper were significantly ($P < 0.001$) more effective in reducing the population of spoilage bacteria on Fassiekh over a 4-day period [79].

The antimicrobial mode of action of *Capsicum*-derived compounds is not clearly elucidated. Moreover, the accumulation of pyruvic acid and the reduction of ATP demonstrated that the extract influences cell membrane permeability, and bacterial respiratory metabolism, which ultimately leads to death. Nevertheless, mode-of-action studies need to be expanded to include a greater variety of microorganisms (bacteria, yeast and molds).

Complexing compounds such as capsaicin with other molecules to make more efficient delivery systems (*e.g.*, microcapsules) may broaden food application potential [80], especially for products in which pungency is not a desirable attribute. Additionally, *Capsicum*-derived extracts could be used in active packaging systems. Achieving greater use of *Capsicum*-derived extracts for food preservation by the food industry requires greater research demonstrating efficacy in complex food systems and demonstration of cost effectiveness.

Biological activities of *Capsicum* plant extracts and their constituents: Potential as a functional ingredient

Antioxidant activity

Among *Capsicum* phytochemicals, carotenoids works as coloring compounds in peppers and exhibits a significant role to provide protection against cells and tissues from harmful reactive oxygen species (ROS), acting as scavengers of singlet molecular oxygen, peroxyl radicals, and reactive nitrogen species (RNS). Nonetheless, much of the total antioxidant activity of *Capsicum* spp. is related to its phenolic content, not only to its vitamin and carotenoid content [13]. Generally, in *C. annuum*, *C. frutescens*, and *C. chinense*, the concentration of antioxidants constituents (carotenoids, flavonoids, phenolic acids, and ascorbic acid) increases during fruit maturation together with the antioxidant activity determined *in vitro* [81]. Moreover, the antioxidant activity of *Capsicum* is higher compared to other vegetables. In this sense, a recent study by Morales-Soto *et al*. (2013) showed that, among 44 cultivars of fruits and vegetables grown in Andalusia (Spain), red ‘California’ pepper (4.550–13.810 mmol eq. Trolox/100 g), ‘Fino’ lemon (11.560–14.340 mmol eq. $FeSO_4$/100 g), and red onion (2.921–13.830 mmol eq. Trolox/100 g) exhibited the highest antioxidant capacity in the TEAC (trolox equivalent antioxidant capacity), FRAP (ferric ion reducing antioxidant power), and ORAC (oxygen radical absorbance capacity) assays, respectively. As a note, this red pepper is a non-pungent and its main constituents are hydroxycinnamic acids, and flavonoid glycosides [13]. However, a potential pro-oxidant effect of *Capsicum* flavonoids may occur in the presence of metal ions in some experiments [81]. Capsaicin has also shown an antioxidant potential comparable to that of butylhydroxyanisole (BHA), being able to protect the oxidation of human low density lipoprotein (LDL), inhibit cooper ion-induced lipid peroxidation decreasing the formation of thiobarbituric acid reactive substance (TBARS) [82]. Another study suggested that the main antioxidant compounds from red hot pepper fruit (*C. annuum*) are sinapoyl and feruloyl glycosides, and the main compound from green pepper is quercetin-3-*O*-L-rhamnoside, together with capsaicin and dihydrocapsaicin [53].

Several studies have examined the antioxidant activity of *Capsicum* spp. on human cells. In this context, lipid peroxidation induced by ascorbic acid and ferrous sulfate in erythrocyte membranes was found to be inhibited by active principles of *C. annuum*, suggesting a defensive mechanism against free radicals and a protective effect on erythrocyte integrity [83]. The phenolic glycosides isolated from *C. annuum* fruit and their aglycones were examined according to their antioxidant activities and their protective abilities against X-radiation on human cell lymphocytes, showing that phenolic glycosides present higher X-ray radioprotective activities than their aglycones [84]. Another study examined the antioxidant properties of different fraction of methanolic extract of unripe fruit part of the

C. annuum var. *conoides* plant [85]. This study showed a dose-responsive induction for antioxidant properties of some fractions, which may be potent natural antioxidant supplements for anti-oral cancer cell treatment through their observed effect on decreasing cell viability of human oral cancer cells (Ca9-22) [85]. Another study showed that capsaicin directly inhibits the growth of human leukemic cells through oxidative stress, involving phosphorylation of p53 at Ser-15 residue by ROS [86]. The binding and cytotoxic activities of extracted polyphenols from bioactive compounds of *C. annuum* correlates with their concentrations [87]. Methanolic extracts from *C. annuum* have been reported to inhibit 4-hydroxy-2-nonenal (HNE)-induced and H_2O_2-induced DNA damage on human leucocytes and human colorectal adenocarcinoma cells (HT-29), suggesting a role as antioxidant and cancer prevention [88].

Concerning the antioxidant activity of *Capsicum in vivo*, a recent study by Morittu *et al*. [89] evaluated the oxidative status of *C. annuum* cv. Fiesta at two ripening stage in CD-1 mice. Their results showed that, at the dose reported by the European Commission as the mean daily consumption of capsaicin, the extracts were well tolerated, independently from the ripening stage. No beneficial effect was seen in terms of antioxidant activity, but at the same time a non-significant increase of ROS production was observed. On the contrary, capsaicin may improve the antioxidant status indirectly [89]. As an example, it was evaluated against carbon tetrachloride-induced liver injury in rats treated for 8 weeks, showing a hepatoprotective effect *via:* decrease of the generation of malondialdehyde, induction of antioxidant systems (superoxide dismutase, catalase, and glutathione-*S*-transferase) and inhibition of active caspase-3 [90].

Chemopreventive activity

Capsaicin has been largely studied due to its potential to induce apoptosis in many different types of cancer cell lines including pancreatic, colonic, prostatic, liver, esophageal, bladder, skin, leukemia, lung and endothelial cells while normal cells are unharmed [91]. However, its role in tumorigenesis remains controversial because both cancer prevention and promotion have been proposed [92]. The promoter effect seems to be related to the consumption of high amounts of capsaicin in the diet. In this sense, a meta-analysis from 2014 suggested a moderate capsaicin consumption due to this dual role [93].

In general, its anticancer activity is through targeting multiple signaling pathways and cancer associated genes at different tumor stages [94]. These mechanisms have been studied *in vitro* and in animal models, as commented below.

A dose-dependent apoptotic effect of capsaicin on human pancreatic cancer cells was assessed in a study performed using *in vitro* and *in vivo* systems [95]. This study suggested the involvement of endoplasmic reticulum stress in the induction of apoptosis in human pancreatic cancer cells by its [95]. Studies performed on tumors formed by human prostate cancer cell cultures grown in mouse models reported that it is able to cause apoptosis and kill prostate cancer cells [96]. Moreover, another mechanism to induce apoptosis of human pancreatic cells is through the decrease of thioredoxin expression and dissociation of thioredoxin/apoptosis signal-regulating kinase 1 (ASK1) [97]. Capsaicin reduces the viability, propagation, and induces apoptotic death in pancreatic neuroendocrine tumor (NET) cells. In addition, it also causes loss of mitochondrial membrane potential, inhibits ATP synthesis, reduces mitochondrial Bcl-2 protein production, increases cytochrome c levels, and minimizes ROS generation [98]. Another study shows that capsaicin leads to induction of apoptosis in human lung cancer cells as well [99].

A study conducted by Amantini *et al*. [100] showed that administration of capsaicin prevented the proliferation of basal carcinoma (BC) cells lines *via* stimulation of the autophagic process, altering redox homeostasis, inducing mitochondrial depolarization, changing adenosine diphosphate/adenosine triphosphate (ADP/ATP) ratio along with activating activated protein kinase (AMPK) pathway. This enhanced capsaicin-induced cell death, demonstrating that capsaicin-induced autophagy acts as a pro-survival process in BC cells. Moreover, capsaicin-treated BC cells displayed typical mesenchymal features of the epithelial mesenchymal transition (EMT) as elongated shape and over-expression of vimentin, α5 and β1 integrin subunits, integrin-like kinase and the anti-apoptotic Bcl-2 proteins. It stimulates upregulation of Dhh/Ptch2/Zeb2 members of the Hedgehog signaling pathway, increases CD24, vascular endothelial growth factor-A (VEGFA) and tissue inhibitors of metalloproteinases-1 (TIMP-1) and decreases CD44 and activates leukocyte cell adhesion molecule (ALCAM) mRNA expression levels [100].

A case-control study conducted in Italy revealed a protective role of chili against stomach cancer [101]. Capsicum is considered a medicinal plant effective against gastric cancer in Mexico [102]. The fruit of *C. annuum* present elevated accumulation of arsenic, which has been reported to show anticancer activity [103]. Several studies have demonstrated dose-dependent inhibitory effects of capsaicin against stomach [104, 105] and colorectal human cancers [106]. In human gastric cell lines, capsaicin induces cell death via bcl-2-sensitive apoptotic pathway [104], overexpression of p53 and/or c-myc genes [107], activation of caspase-3 [108], and inhibits cell proliferation by cytochrome c release [105]. Moreover, capsaicin enhances the potential effectiveness of other chemotherapeutic agents on Korean human gastric cancer cell line, increasing apoptotic cell death of cisplatin-resistant gastric cancer cells after co-treatment with cisplatin [109]. In human colorectal cancer cells *in vitro*, capsaicin suppressed cell proliferation involving the suppression of transcriptional activity of β-catenin [106]. Moreover, capsaicin provokes apoptosis cell death on human colon cancer thought the activations of caspase-3, -8 and -9 and down-regulation of anti-apoptotic bcl-2 and up-regulation of pro-apoptotic bax proteins [110]. Furthermore, capsaicin also inhibits human colon cancer *via* inducing cell cycle G0/G1 phase arrest and apoptosis, stabilizing and activating p53 [111].

Furthermore, carotenoids isolated from the fruit of red paprika *C. annuum* showed potent *in vitro* anti-tumor-promoting activity through inhibitory effects on Epstein-Barr virus early antigen activation [112]. A protein fraction containing DING proteins, which have a great biological importance due to their ability to inhibit carcinogenic cell growth, is present in *C. chinense* [113, 114]. Moreover, these proteins also inhibit the growth of several plant and human pathogenic bacteria [114].

Anti-diabetic potential

Many studies have reported both *in vitro* and *in vivo* different effects of *Capsicum* on glucose metabolism. Selected pungent and non-pungent *Capsicum* varieties have shown high antioxidant activity and an excellent inhibitory profile on carbohydrate-degrading enzymes such as α-glycosidase, which is related to glucose absorption. In this study, the most anti-diabetic potential was shown by the sweet varieties, not for the pungent ones [115]. Nevertheless, the combination of different chilis (as is habitual in the diet) seems to increase these activities [116]. Regular consumption of hot *Capsicum* spp. may improve postprandial glucose, insulin, and energy metabolism [117]. Others studies have found that *C. chinense* (habañero) showed higher activity against α-amylase than α-glucosidase [118]. The crude extract from different varieties of *Capsicum* oleoresin showed potent antioxidant and antidiabetic activities [119]. In this study, the antidiabetic effect was assessed against α-amylase inhibitory activity [119]. *C. baccatum* seeds also inhibited mammalian α-amylase activity [120]. Another species of *Capsicum*, *C. frutescens*, presents antioxidant and antiglycation properties [121]; the accumulation of advanced glycation end products in the body is associated with diabetes mellitus.

In humans, the effect of 5 g of *C. frutescens* on plasma glucose level was studied in 12 healthy volunteers by performing the oral glucose tolerance test [122]. The results of this study showed that the *Capsicum* dose decreased plasma glucose levels at 30 and 45 minutes and, moreover, increased plasma insulin levels at 60, 75, 105, and 120 minutes. This study concludes that *C. frutescens* might have clinical implications in the management of type 2 diabetes mellitus decreasing plasma glucose and maintaining insulin levels [122]. Similar effects of 5 g ingestion of *C. frutescens* has been reported on plasma glucose in healthy Thai women [123]. Moreover, this study evaluated the effect of chili pepper on metabolic rate in 12 women, showing an immediately increase of metabolic rate after ingestion and sustained up to 30 min [123]. However, a randomized controlled study performed with 100 mL juice of *C. annuum* var. *grossum* for 4-consecutive days, on 15 subjects with type 2 diabetes mellitus under yoga therapy, showed no difference in blood glucose level (fasting or postprandial) between control and experimental groups [124]. In the case of chili, its consumption provokes a decrease of insulin resistance reflecting a postprandial homeostasis model assessment of insulin resistance in a Chinese population [125]. The supplementation of 5 mg/d of capsaicin for 4 weeks improved postprandial hyperglycemia, hyperinsulinemia and fasting lipid metabolic disorders in women with gestational diabetes mellitus [126]. Overproduction of insulin after meals could result in insulin resistance; chili intake reduces this overproduction and may reduce the risk in insulin resistance [127]. Moreover, the type of chilis may influence insulin resistance more than their quantity [124].

Gastroprotective potential: anti-ulcer and antimicrobial activity

Gastrointestinal diseases may be caused by various factors such as alcohol, acetic acid, nonsteroidal anti-inflammatory drugs (e.g., aspirin, indomethacin and ibuprofen), *Helicobacter pylori*, gastric acid, pepsin and inflammatory cytokines. Moreover, ROS are known to be involved in gastrointestinal diseases [128].

In general, spices have been recognized for their digestive stimulant action because they can intensify salivary flow and gastric juice secretion and help digestion when the nerve centers are stimulated by the sense of smell and by the presence of pungent principles such as capsaicin [129]. The hot *Capsicum* digestive stimulatory action is supposed to be related to the stimulation of saliva and bile secretion as well as digestive enzymes activities of the pancreas and small intestine. It also stimulates the saliva production and the salivary amylase activity, which helps to digest starch, as well as the mucous membrane production in mouth, throat and gastrointestinal tract. Animal studies have found that hot *Capsicum* enhances the fat digestion and absorption in high fat fed animals through the stimulation of the liver to secrete bile rich in bile acids [58].

Chili extracts, capsaicin and its other phytochemicals regulate the intestinal transport system for various food nutrients, increasing the permeability of intestinal epithelial cells [130], and enhance the rate of gastric emptying [131]. In view of irritant and likely acid-secreting nature provoked by chili ingestion, it is being avoided in persons with ulcers. *C. frutescens* extract present concentration-dependent cytopathic effect on oral mucosal fibroblasts [132]. However, various studies with chili extract and capsaicin have revealed protective roles versus injurious influence on gastric mucosa [128]. Therefore, the mechanism involved in gastric mucosa protection by chili and its phytochemical constituents may involve the activation of gastrointestinal transient receptor potential vanilloid subtype 1 (TRPV1), antioxidant enzymes and inhibition of inflammatory factors [133]. Capsaicin inhibits acid secretion, prevents and heals ulcers by disposing of acid from the stomach by stimulation of alkali, mucus, bicarbonate secretions and gastric mucosal blood [134-136]. Treatment with red pepper and capsaicin-containing red pepper decreases dyspeptic symptoms, epigastric pain, fullness, nauseas and heartburn in dyspeptic and heartburn patients [137-139]. Moreover, capsaicin decreases esophageal symptoms in different gastroesophageal reflux disease patients such as Barrett's esophagus [140].

An epidemiological study, performed with 103 Chinese patients with peptic ulcer and 87 Malaysians and Indians controls, has found that chili use has a protective effect against peptic ulcer disease [141]. A prospective study of 84 healthy human subjects has evaluated the gastroprotective effect of capsaicin against two models of induced gastric mucosal damage, by ethanol or indomethacin [142]. The results of this study show that small doses of capsaicin (1-8 µg/100 mL) have gastroprotective effect against injures by ethanol or indomethacin and suggest that is attributed to stimulation of the sensory nerve endings [142]. Other study, performed on 18 healthy volunteers, reported that the administration of 20 g chili orally with 200 mL water decreases the severity of acute aspirin-induced gastroduodenal mucosal injury [143]. Moreover, capsaicin has been described as a new potential gastroprotective therapeutic drug in healthy humans, in patients with mucosal damage and in diseases requiring treatment with nonsteroidal anti-inflammatory drugs [136].

Capsaicin may induce motility in the gastric antrum, duodenum, proximal jejunum and colon which helps to diminish functional dyspepsia. However, clinical studies on its efficacy in gastro-oesophageal reflux disease and dyspepsia are limited, and there is limited information regarding the effect of chronic capsaicin ingestion in both diseases. So, a randomized double-blinded study in 30 functional dyspepsia patients using 1.75 mg of capsaicin ingestion for 5 weeks demonstrated that it significantly improved overall symptoms of epigastric pain, fullness, and nausea but not epigastric burning, bloating and belching compared to placebo [144].

Furthermore, various phytochemicals of *Capsicum* spp. present antimicrobial activity and have been described as protectors against gastric pathogens [133, 145-147]. Chili inhibited the growth of foodborne gastrointestinal pathogens such as *Salmonella typhimurium*, *Listeria monocytogenes*, *Bacillus cereus* [148], *Proteus mirabilis*, *Pseudomonas aeruginosa*, *S. aureus*, *E. coli* [133, 145, 149-151] and *Vibrio cholerae* [152, 153]. Moreover, isolated compounds from chili have been found effective against few types of pathogenic yeasts [120, 151, 154] and fungi [155, 156]. *H. pylori* is an important causal factor in gastric and duodenal ulcers and is associated with the development of gastric cancers. *In vitro* studies showed that capsaicin inhibited the growth of this pathogenic bacteria [133, 157] suggesting that chili could prove to be a therapeutic agent for *H. pylori*-induced gastrointestinal disease.

Pain relief

Natural capsaicinoids of chili peppers have received considerable attention as topical pain relievers [128, 158]. This unique property of capsaicin has been exploited by the use of creams, ointments, and patches to treat many types of pain, especially the neuropathic type [159]. Two trials performed with topical application of creams containing 0.075% [160] or 0.025% [161] of capsaicin showed analgesic effect in 21% and 70% patients with osteoarthritis and rheumatoid arthritis, respectively. In a study involving investigators of 12 sites and 219 men and women with painful diabetic neuropathy, topical application of 0.075% capsaicin reduced pain with subsequent improvement in daily activities, enhancing the quality of the patient's life [162]. The repeated application of a low dose capsaicin cream (0.075%), or a single application of a high dose patch (8%), seems to provide a degree of chronic neuropathic pain relief in adults [163, 164]. A single application of capsaicin 8% patch for 60 minutes produced effective pain relief for up to 12 weeks in patients with neuropathic pain, suggesting that high-concentration capsaicin path have the advantages of longer duration of effect and low risk for systemic effects [164]. Moreover, capsaicin creams are used to treat psoriasis, reducing inflammation and itching [165, 166]. The use of 8% capsaicin patch has demonstrated its efficient and sustained pain relief in post-herpetic neuralgia pain, a painful condition that occurs after reactivation of the dormant herpes zoster virus [167]. However, the side effects are consistently higher in all studies about neuropathic relief with capsaicin, but the significance of safety data was not quantified, and it is not clear if topical capsaicin should be used as a first-line treatment [168]. In focal pain conditions, capsaicin may be given successfully by injection to knock out nociceptors and achieve pain control in single doses applications to alleviate the pain condition for months in Morton's neuroma and arthritis, but its major weakness is the immediate burning sensation lasting minutes to hours [169].

The mechanisms of pain relief action of topical capsaicin involve the transient receptor potential cation channel subfamily V member 1 (TRPV1), also known as the capsaicin receptor and the vanilloid receptor [158, 170]. Capsaicin selectively activates TRPV1, Ca^{2+} permeable cationic ion channel which is enriched at the terminals of certain nociceptors. Activation is followed by a prolonged decrease response to noxious stimuli [169].

Potential role in the metabolic syndrome

Metabolic syndrome is referred to the clustering of insulin resistance, hypertension, dyslipidemia, and obesity, and this condition has been associated with increased risk of cardiovascular diseases and type 2 diabetes in adults. *Capsicum* spp. and their constituents may be of interest to prevent or treat some of these conditions, being revised in this section.

The risk of having metabolic syndrome is closely linked to overweight and obesity. In humans, the potential benefits of capsaicinoids for weight managements are the increase of the energy expenditure, the enhancement of lipid oxidation and the appetite reduction [171]. The number of studies on weight management is large, while the mechanism of action for appetite reduction has been less studied. In this sense, a randomized double-blind placebo-controlled study, performed with 91 moderately overweight subjects, showed that capsaicin (135 mg/day) increased fat oxidation during weight maintenance which seems to lead to a decrease in appetite as well as a decrease in food intake [172]. A study that investigated the effects of regular consumption of chili on *in vitro* serum lipoprotein oxidation in healthy adult men and women conclude that regular consumption of chili resists serum lipoprotein oxidation [173]. Conversely, another study performed on long distance male runners 18-23 years of age reported an increased carbohydrate oxidation at rest and during exercise [174].

In studies conducted in humans it was observed that red pepper induced a reduction of *ad libitum* food intake and an increased postprandial energy expenditure and lipid oxidation [123, 175-178]. After a chili meal, a reduced energy expenditure was noted in adult men and women with body mass index ≥ 26 [173] and postprandial respiration quotient was reduced by 30% [179, 180]. This reduction on respiration quotient was observed in dietary consumption of chili among habitual users and non-users of chili [181]. In a study performed with 12 men and 12 women, the exposure to capsaicin, oral and gastrointestinal, increased satiety and reduced caloric as well as fat intake [182]. Moreover, oral exposure provoked a stronger reduction suggesting that capsaicin has sensory effects [182]. Capsaicin has been shown to be effective on obesity management in some short-term studies, however, the long-term use of capsaicin may be limited by its strong pungency [183]. A larger increase in energy expenditure was observed in men after a meal containing 10 g of red pepper, and the author of this study suggest that it was caused by beta-adrenergic stimulation [177]. Chili consumption increases diet-induced thermogenesis in a high fat and carbohydrate diet [179, 184], but was more pronounced in irregular consumers of chili than habitual consumers [181]. In a 2-weeks study, a supplement containing 0.4 mg capsaicin, 625 mg green tea extract and 800 mg essence of chicken reduced body fat content of free-living healthy human subjects, approximately 460 g, and increases the resting energy expenditure [185].

A possible solution to avoid the pungency of capsaicin in long-term studies is use of non-pungent analogs. The effect of CH-19 sweet pepper, a non-pungent cultivar of red pepper, was investigated on oxygen consumption and body temperature in 11 healthy volunteers. As a note, it presents capsiate, which has a structure similar to capsaicin but without pungency [186]. The results of this study showed that this type of pepper increased thermogenesis, forehead, body surface and neck temperature, and energy consumption [186]. The effects of 9 mg capsaicinoids ingestion, extracted from pepper fruit variety CH-19 sweet, were examined in a study on energy expenditure to analyze its relation on brown adipose tissue in 18 healthy men [187]. The results suggested that capsaicinoids increase energy expenditure through the activation of brown adipose tissue [187].

However, the efficacy of these bioactive compounds in weight loss is not conclusive. In fact, no solid evidence shows that capsaicin ingestion provokes weight loss, but there is a positive correlation between capsaicin and a decrease in weight regain [128]. Mean short-term studies have demonstrated an increase in diet-induced thermogenesis and a decrease in the respiratory quotient immediately after a meal in which capsaicin was supplemented (Yoshioka *et al*., 1995). Long-term studies (three months) showed a limited effect on weight regain after a model of weight loss [188]. The effect on energy expenditure is marginal, around 50 kcal /day [171]. These results were the basis of the European Food Safety Agency report [189] to assume that the consumption of capsaicin has no effect on body weight maintenance after weight loss.

Both capsaicin and capsaicinoids are capable of increasing the whole-body energy expenditure and reduce the body fat *via* brown adipose tissue stimulation through the specific receptor TRPV1, increasing the stamina consumption and decreasing body fat modestly but consistently [190]. Besides other factors, the *trans*-differentiation of mesenchymal stem cells into adipocytes is an added detrimental factor that may cause the intensification of obesity. Thus, Ibrahim *et al*. [191] have recently determined whether capsaicin is capable of inhibiting the differentiation of bone marrow mesenchymal stem cells (BMSCs) to adipocytes *in vitro*. BMSCs were exposed to different capsaicin concentrations for a period of 6 days following 2 days of adipogenic induction. The capsaicin exposed cells were collected at three different time points (2, 4 and 6 days) and subjected to various analyses. After capsaicin exposure, dose- and time-dependent reduction in cell viability and proliferation was observed in BMSCs. Interestingly, although capsaicin is considered an antioxidant compound, it increased the production of ROS and RNS in order to induce cell cycle arrest at G0-G1 along with increased apoptosis. Capsaicin exposure significantly inhibited the early adipogenic differentiation, lipogenesis and maturation of adipocytes with concomitant repression of PPARγ, C-enhancer-binding proteins (C/EBPα), fatty aid binding protein-4 (FABP4) and stearoyl-CoA desaturase-1 (SCD-1). Capsaicin-based stimulation for ROS and RNS production potentially inhibits the adipogenic differentiation of mesenchymal stem cells *via* many different pathways, *i.e.*, anti-proliferative, apoptotic and cell cycle arrest [191].

Several studies have documented the beneficial influence of capsaicin on lipid metabolism, especially as an antihypercholesterolemic agent, and anti-diabetic properties, commented before. In the obese diabetic model ob/ob mice, capsaicin (0.01-0.02% in the diet for 6 weeks) significantly suppressed the enhancement in fasting blood glucose, as well as also increased the insulin levels. Moreover, capsaicin significantly increased the fecal butyrate and plasma total GLP-1 levels, but decreased plasma total ghrelin, TNF-α, IL-1β, and IL-6 levels [192]. Capsaicin also reduced body weight *via* activating transient receptor potential vanilloid 1 (TRPV1) cation channel, improving glucose tolerance, up-regulating the expression of Mucin 2 gene Muc2 and antimicrobial protein gene Reg3g in the intestine of C57BL/6 mice [193]. In atherosclerotic plaque mice, treatment with dihydrocapsaicin supplementation momentously showed significant reduction in cellular cholesterol content, enhancement in apoA1-mediated cholesterol efflux. In addition, it also lowered the low density lipoprotein, plasma triglyderides, very low density lipoprotein, interleukin-6 (IL-6), interleukin-beta (IL-1β), C-reactive protein (CRP), and tumor necrosis factor (TNF-α) levels, whereas it enhanced high density lipoprotein [194]. Moreover, capsaicin has shown to be hypotriglyceridemic, thus preventing accumulation of fat in liver under adverse situations by enhancing triglyceride transport out of the liver also in animal models [195]. Also, it has been reported the capacity of capsaicin to reduce adiposity in rats.

Concerning cardiovascular effects, a recent study performed on a rat model of metabolic syndrome suggested that capsaicin (0.5-1 mg/kg body weight for 14 d) promoted global improvement of cardiovascular autonomic control. It determined heart variability improvement, increased vascular sympathetic drive and increased α-index (spontaneous baroreflex sensitivity). However, this treatment did not improve lipid and glucose abnormalities [196] .

Other potential health benefits

Capsaicinoids and other bioactive compounds from *Capsicum* seem to have other health benefits when assayed in animal models:

- A supplementation with capsaicin may improve physical activities, including grid, strength and endurance performance by increasing live glycogen content. Also, it can ameliorate some exercise-induced related fatigue parameters in animal studies [197].
- The presence of hot chilies in the normal diet has been related to a better iron status in the population [198].
- Capsaicinoids but not capsinoids may decrease the total plasma cholesterol, reduce the formation of atherosclerotic plaque and relax the aortic artery increasing the fecal excretion of acidic sterols in hamsters fed with diets containing capsaicinoids. Moreover, it may modulate plasma lipids and possess beneficial vascular activity [199].
- A study aimed to examine various treatments for knee osteoarthritis on older humans reported that capsaicin, orally or locally, reduces rheumatoid arthritis pain, inflammatory heat and noxious chemical hyperalgesia [200]. In human polymorphonuclear leukocytes cells it is reported that capsaicin modulate 5-lipoxygenase, the key enzyme involved in the biosynthesis of the inflammatory mediators leukotrienes [201].

Conclusions

This review highlights that *Capsicum* and dietary capsaicinoids have intriguing potential for health promotion. In this sense, several scientific studies have provided evidence for their beneficial effects *in vitro*, *in vivo* and in humans against cancer, diabetes, gastrointestinal diseases, and pain. Moreover, the multifunctional properties of *Capsicum* and capsacin seem to be promising for the prevetion/treatment of the metabolic syndrome. This includes weight management properties, antidiabetic potential, hypocholesterolemic and hypotriglyceridemic activity, and beneficial cardiovascular effects. Although most of these studies are still not conclusive and only focused on capsaicin, they may be the basis of the formulation of new pharmacological active ingredients to be used in pharmaceuticals and functional foods. This also requires the definition of the dose and target population.

The application of phytochemicals derived from *Capsicum* plants for food preservation and safety is also promising. Coupling for example capsaicin and dihydrocapsaicin with non-thermal processing methods, with other natural antimicrobials or salt, may provide to consumers with safer products, which do not contain chemical preservatives. Nevertheless, the required doses, the processing time of the applied non-thermal method and the sensory properties should be evaluated in each food. This is an avenue of future research of other non-pungent *Capsicum* constituents that deserve further studies.

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Accounts/Reviews

Natural Product Communications
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Volume 13, Number 11

Contents

Continued inside backcover