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Phytochemical constituents and biological properties of domesticated capsicum species: a review

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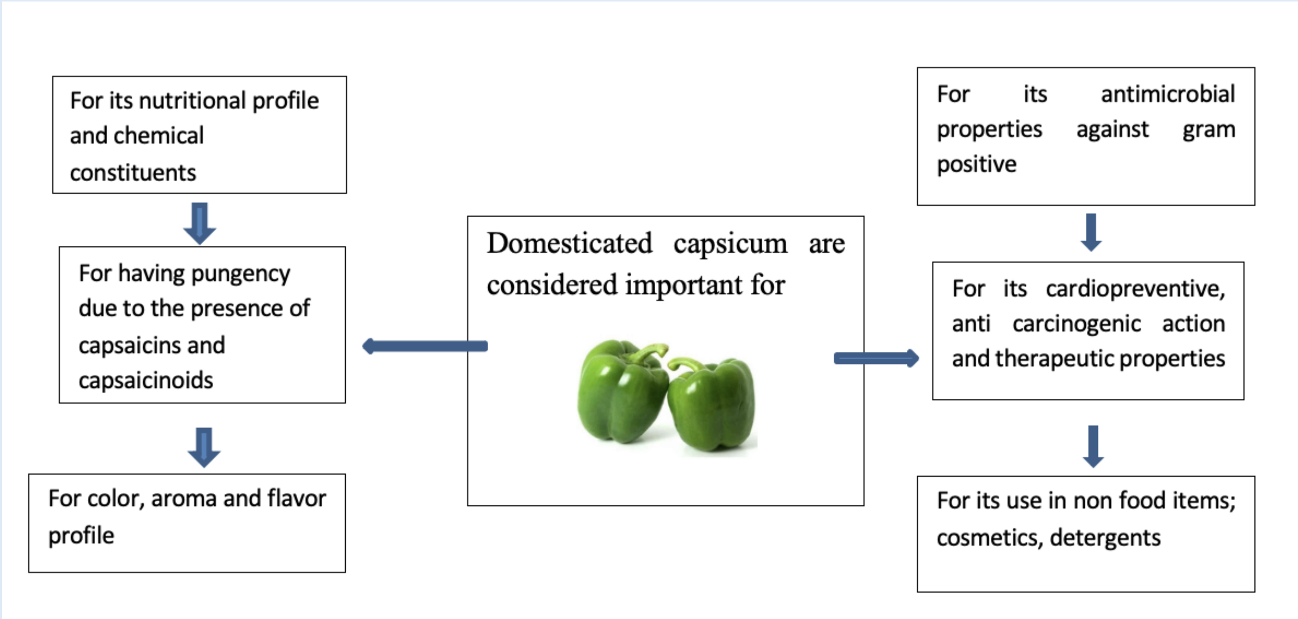
ABSTRACT

Pepper (Capsicum spp) is cultivated and consumed in almost every region of the world both as fresh vegetable and dried spice. Capsicum and its different varieties possess many valuable properties which distinguish them from other vegetables and in many food items as a spice for its strong pungent flavor that is produced during the secondary metabolism of the plant.

Capsicum fruit exhibits a multiple color profile due to the presence of carotenoids which can be used as a natural coloring agent and antioxidant. Almost all the parts of the capsicum are considered a rich source of health-related bioactive compounds including polyphenols, flavonoids, and other aromatic compounds. One of the important biological properties of capsicum is its ability to act as antioxidants to reduce oxidative stress leading to the prevention of several degenerative diseases. The functional compounds of capsicum exhibit excellent antimicrobial properties, particularly against gram-positive pathogenic microorganisms. The nutraceutical functionality of phytogenic compounds obtained from capsicum also confirms the anticarcinogenic and cardio-preventive effectiveness. The essential oils from capsicum are also being used as anti-aging substances in cosmetic products.

Accordingly, this article is an attempt to provide an overview of the chemical and functional properties of the bioactive compounds sourced from capsicum and their effective utilization in the medicine, food, agricultural, cosmetic, and textile industries.

Keywords: Capsicum, capsaicinoids, capsaicin, carotenoids, pungency



INTRODUCTION

Capsicum, commonly called pepper, is an annual herbaceous plant and a member of the family Solanaceae. Noted for its pungency, aroma, and color characteristics, *Capsicum annuum* L. is the most widely grown spice in the world. It is a member of the genus Capsicum that includes close to 30 species and is one of the five domesticated species, others being *C. baccatum* L., *C. chinense* Jacq., *C. frutescens* L., and *C. pubescens* [1, 2]. A native of the Americas, where it has been cultivated for thousands of years, the plant spread to other parts of the world following European colonization and trade activities. *C. annuum* is also widely cultivated in various tropical, subtropical, as well as temperate regions of the world, and has been a part of the human diet since 7500 BC [2]. The genus is of considerable economic significance as both hot and sweet chili pepper cultivars are cultivated and consumed as both fresh vegetables and as a spice [3, 4].

Apart from its use as a culinary commodity, *C. annuum* has also been a subject of pharmacological research due to the presence of various chemical compounds with potential therapeutic properties [4]. The chemical profile, however, varies due to various factors, such as species, seasonality, environmental conditions, as well as the life cycle of the plant [5]. Capsicum has also proved to be very beneficial due to its use in the form of traditional remedies for the cure of various ailments such as ulcers, toothache, rheumatism, alopecia, and diabetes [6]. Capsicum fruit is also unique in chemical composition as it contains phenolic compounds, flavonoids, alkaloids, and carotenoids, that have beneficial effects on human health [7]. Moreover, a host of studies have reported that capsicum seeds are rich in proteins, essential fatty acids, dietary fiber, and minerals, nutritional components highly beneficial for the improvement of human health [8]. Furthermore, various vitamins such as vitamin C, vitamin A, vitamin E, and folate have also been reported in significant amounts in *C. annuum* [9]. The five major domesticated and economically significant capsicum species are presented in Fig 1.

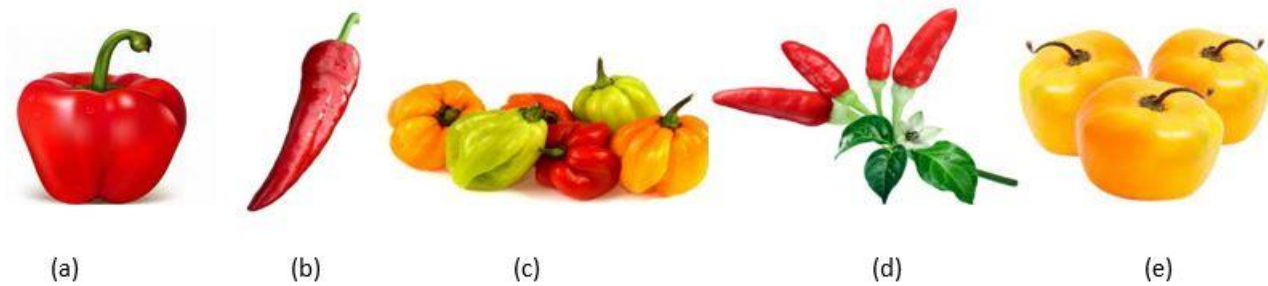


Figure 1. Capsicum fruits and its major species[28]; a) *C. annuum (*Sweet bell pepper*), b) C. baccatum (*aji pepper*), c) C. chinense (*bhut jolokia pepper*), d) C. frutescens (*bird's eye chilli*), e) C. pubescens (*rocoto pepper*)*

NUTRITIONAL PROFILE AND CHEMICAL COMPOSITION OF CAPSICUM

C. annuum is a rich source of carbohydrates, with reducing sugars, notably, glucose and fructose predominant over the non-reducing sugars (sucrose) [10]. The dietary fiber content for almost all the *C. annuum* varieties was found to be significant, and it remained consistent through various developmental stages of the plant. A varied amount of protein was reported among different varieties of capsicum. The concentration of proteins was negatively affected by the increased concentration of carbon dioxide (CO_2) in the atmosphere, whereby an increase in the levels of sugars (both reducing and non-reducing) and fiber was observed by these elevated concentrations of CO_2 [10].

Capsicum is also a good source of many water-soluble and fat-soluble vitamins including vitamin B complex, ascorbic acid (vitamin C), vitamin A and β-carotenes, as well as a significant amount of minerals including zinc, iron, calcium, potassium, sodium, and sulfur [11]. The detailed proximate composition of *C. annuum and C. chinense* is highlighted in Table 1.

Table 1: Chemical composition of the *Capsicum annuum and Capsicum chinense*

Nutrient	*Capsicum annuum (In 100 g sample)*	*Capsicum chinense (In* **100 g of sample)**	References
Water	8.2 g	8.43g	[11, 12, 73]
Energy	5.724 Kcal	-	[11, 12]
Carbohydrate	47.23 g	50 g	[11, 12, 73]
Fiber, total dietary	33.17 g	29.26 g	[11, 12, 73]
Protein	11.22 g	8.2 g	[11, 12, 73]
Total lipid (Fat)	2.1g	5.06 g	[11, 12, 73]
Saturated fatty acids	0.059 g	-	[11, 12]
Monounsaturated fatty acids (MUFA)	0.050 g	-	[11, 12]
Total ash content	6.26 g	7.33 g	[11, 12, 73]

Nutrient	*Capsicum annuum* *(In 100 g sample)*	*Capsicum chinense* *(In 100 g of sample)*	References
Calcium (Ca)	80.16 mg	60.12 mg	[11, 12, 73]
Iron (Fe)	7.73 mg	4.12 mg	[11, 12, 73]
Sodium (Na)	22 mg	36 mg	[11, 12, 73]
Cupper (Cu)	0.007 mg	-	[11, 12]
Phosphorous (P)	5.274 mg	-	[11, 12]
Selenium (Se)	0.158 mcg	-	[11, 12]
Manganese (Mn)	0.036 mg	-	[11, 12]
Magnesium (Mg)	2.736 mg	-	[11, 12]
Zinc (Zn)	15.78 mg	39.64 mg	[11, 12, 73]
Potassium (K)	6925 mg	5041mg	[11, 12, 73]
Thiamin (Vitamin B1)	0.006 mg	-	[11, 12]
Riboflavin (Vitamin B2)	0.017 mg	-	[11, 12]
Niacin (Vitamin B3)	0.157 mg	-	[11, 12]
Vitamin B6	0.037 mg	-	[11, 12]
Ascorbic acid (Vitamin C)	1.375 mg	-	[11, 12]

Almost all the varieties of capsicum (green, sweet, and hot) are rich in important phytochemicals such as flavonoids and polyphenols that can be regarded as bioactive food ingredients. Other phytochemicals present in capsicum include glycosides and aglycones such as quercetin, myricetin, luteolin, kaempferol, and apigenin [12]. Whereas, glycosides are naturally present in plants' secondary metabolites and are catalyzed by the glycosyltransferase enzymes. Glycosides are composed of two functionally independent parts aglycone and glycone (sugar moiety) which are weakly linked together by glycosidic linkage. These glycosidic linkages can be of different types such as O-glycosides (if the glycosidic linkage formed via oxygen) most abundant plants glycosides, C-glycosides (if the glycosidic bond is with carbon), this linkage is most resistant to hydrolysis [13].

Many studies have been conducted for the identification of carbon and oxygen glycosides using techniques including mass spectrometry fragmentation, and ultraviolet spectral analysis. The results of these studies indicate the presence of four different types of quercetin (3O-rhamnoside,3-*O*-rhamnoside-7-O-glucoside, 3-O-glucoside-7-*O*-rhamnoside, and quercetin glycosylated), two luteolin *O*-glycosides (apiosyl-acetyl-glucoside and 7-*O*-2-apiosyl-glucoside), five luteolin-C-glycosides (6-C-hexoside, 8-C-hexoside, 6-C-pentoxide-8-C-hexoside, 6-C-hexoside-8-C-pentoside, and 6-8-di-C-hexoside), and two apigenin C-glycosides (6-C-pentoside-8-C-hexoside and 6-8-di-C-hexoside) in capsicum [14-16].

The amount of different bioactive compounds in capsicum fruits varies according to the species, genetic properties, growth, and developmental stages, as well as ecological conditions. The red color fruits of capsicum cultivars exhibit the highest level of bioactive compounds, among all the fruits of this family and green color fruits are rich in quercetin 3-O-R-L-rhamnopyranoside which concentration get down during the process of ripening.

However, in the case of capsicum, the bioactive compounds are present in significantly adequate levels and are responsible for many cellular and physiological activities [12]. Some species of red and purple capsicum also contain anthocyanin andthe major anthocyanin present in these fruits is delphinidin-3-trans-coumaroylrutinoside5-glucoside, whereas, the total anthocyanin amount present in fruits ranges between 0.5 mg 100 g $^{-1}$ and 28 mg 100 g $^{-1}$ in ripe yellow to ripe red fruit respectively [17].

PUNGENCY – A CHARACTERISTIC TRAIT OF CAPSICUM

Pungency ('heat') is the prime characteristic of almost all the capsicum varieties and can be attributed to the wider appeal of the plant's utilization as a spice. The two genes that have been discovered to be the determinative factors for the production of pungency in capsicum are Pun1 and pAMT [18]. This appealing property of pungency develops in the capsicum plants during the secondary metabolism when plants produce various beneficial chemicals for humans by way of either of the two pathways, i.e. the phenylpropanoid, and the branched-chain fatty acid pathways [19]. The class of alkaloids that are biosynthesized and ultimately accumulate in the placental tissue during secondary metabolism in capsicum is capsaicinoids and are the principal components responsible for the pungency in chili peppers. The major representative groups of capsaicinoids involved in pungency are capsaicin and dihydrocapsaicin [20].

Capsaicin(*trans*-8-methyl-N-vanillyl-6nonenamide), a HVA derivative, is a hydrophobic, colorless, and odorless compound, and can act as a deterrent against herbivores, and microbial and fungal attacks [21]. Large concentrations of capsaicin are present in placental tissue (where the seeds attach), inner membranes, while to a lesser extent, in the fleshy parts of the fruit [22]. The minor capsaicinoids found in chili fruits include nordihydrocapsaicin (7.4%), norcapsaicin, homocapsaicin I, homodihydrocapsaicin I (2%), homocapsaicin II (2%), homodihydrocapsaicin II, and nonivamide [23]. The degree of pungency in the Capsicum plant is directly proportional to the concentration of capsaicinoids present, in particular, the capsaicins [4, 23]. An alteration in the acid portion of the capsaicin has been associated with the production of analogs with varying degrees of pungency in capsicum fruits [7].

Among the domesticated species of the genus capsicum, the fruit of *C. chinense* is regarded as the most pungent [7]. The level of pungency in hot pepper can be determined by using the (SHV), which acts as an indicator of the number of capsaicinoids present in the sample (the higher the SHV value, the higher will be the pungency of the pepper). In this test, the sample of hot peppers was presented to the panel of 5 trained people. These people record the hot flavor intensity of the provided chili sample. The provided chili sample is diluted to the level at which pungency becomes undetectable, and this dilution is expressed as the Scoville Heat Unit (SHU). The study also reported that among all the capsaicinoids, capsaicin and dihydrocapsaicin showed the most burning flavor and both of these capsaicinoids are responsible for 90% of the total pungency of the capsicum [24].

Capsinoids are the other group of secondary metabolites produced in various species of capsicum, albeit, they are the non-pungent analogs of capsaicin, and therefore due to this characteristic, have various medical applications [5]. The three major capsinoids associated with chili pepper fruits include capsiate, dihydrocapsiate, and nordihydrocapsiate, all of which have exhibited anti-oxidative and anti-inflammatory properties [20]. The chemical structures of major bioactive components are highlighted in Figure 2.

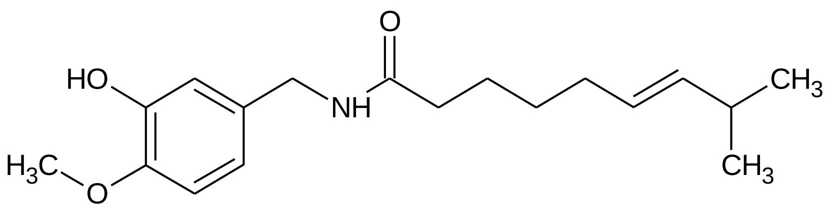


Figure 2a. Structure of capsaicin ($C_{18}H_{27}NO_3$).

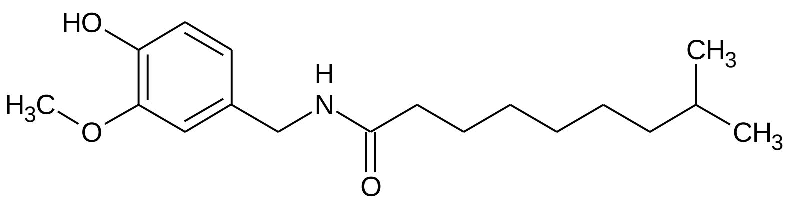


Figure 2b. Structure of dihydrocapsaicin

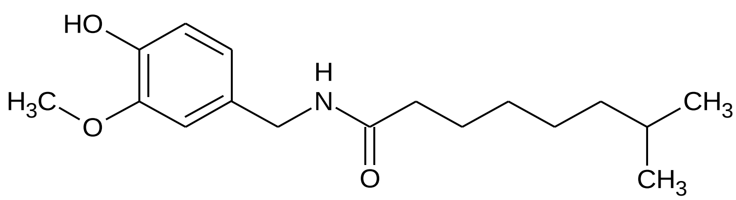


Figure 2c. Structure of nordihydrocapsaicin

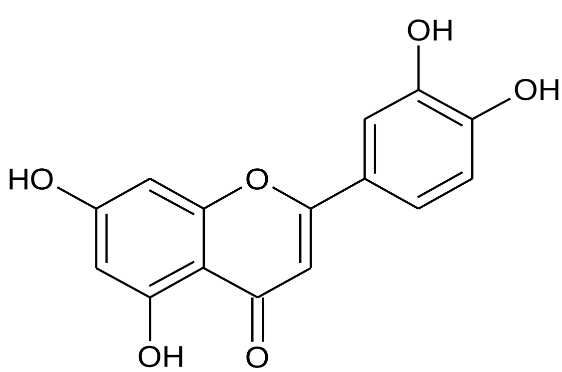


Figure 2d. Structure of luteolin

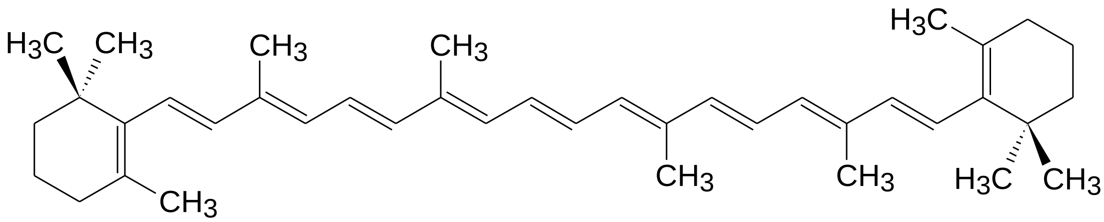


Figure 2e. Structure of carotenoids

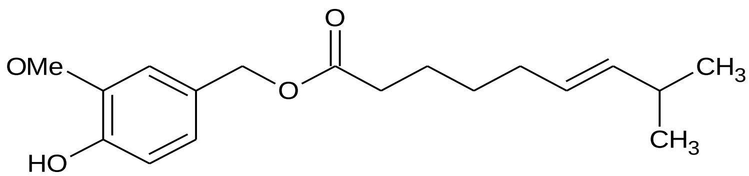


Figure 2f. Structure of capsiate

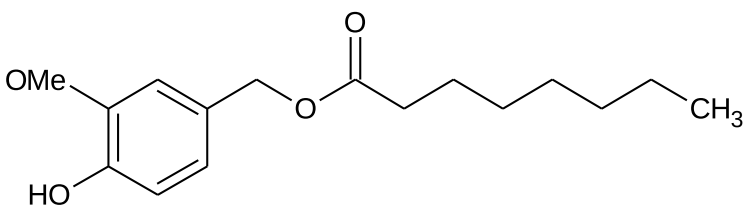


Figure 2g. Structure of nordihydrocapsiate

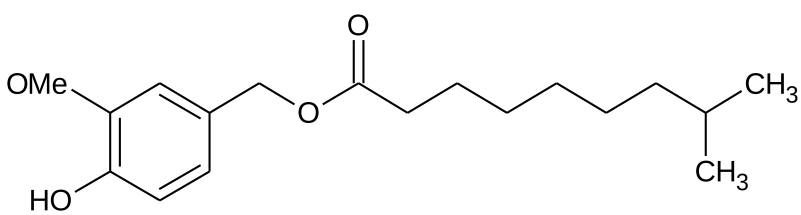


Figure 2h. Structure of dihydrocapsiate

Synthesis and accumulation of pungent compounds:The synthesis of capsaicinoids takes place in the placental tissues, pericarp, seeds, and other vegetative organs including stems and leaves of *the* capsicum plant. Most of the capsaicinoids are formed during the initial phases of the fruit development, i.e. about 20 to 50 days after the anthesis, and this rate of synthesis of capsaicinoids increases as the fruit matures [23].

The other factors which also contribute to the production of capsaicinoids include genotype, fruit maturity, as well as environmental factors such as water availability and solar energy [23]. As mentioned earlier, the two pathways by which capsaicinoids are biosynthesized are the phenylpropanoid pathway and the branched-chain fatty acid pathway.

The primary precursor phenylalanine of the phenylpropanoid pathway is condensed with the primary precursor, valine (or leucine) of the fatty acid pathway, and produces vanillylamine, which plays a key role in the formation of capsaicinoids, and their eventual accumulation in the placental tissue of the fruit [25]. There are many putative enzymes and codifying genes associated with the biosynthesis of the capsaicinoids, however, their complete characterization has not been achieved yet [25]. The model pathway for capsaicin synthesis is represented in Figure 3.

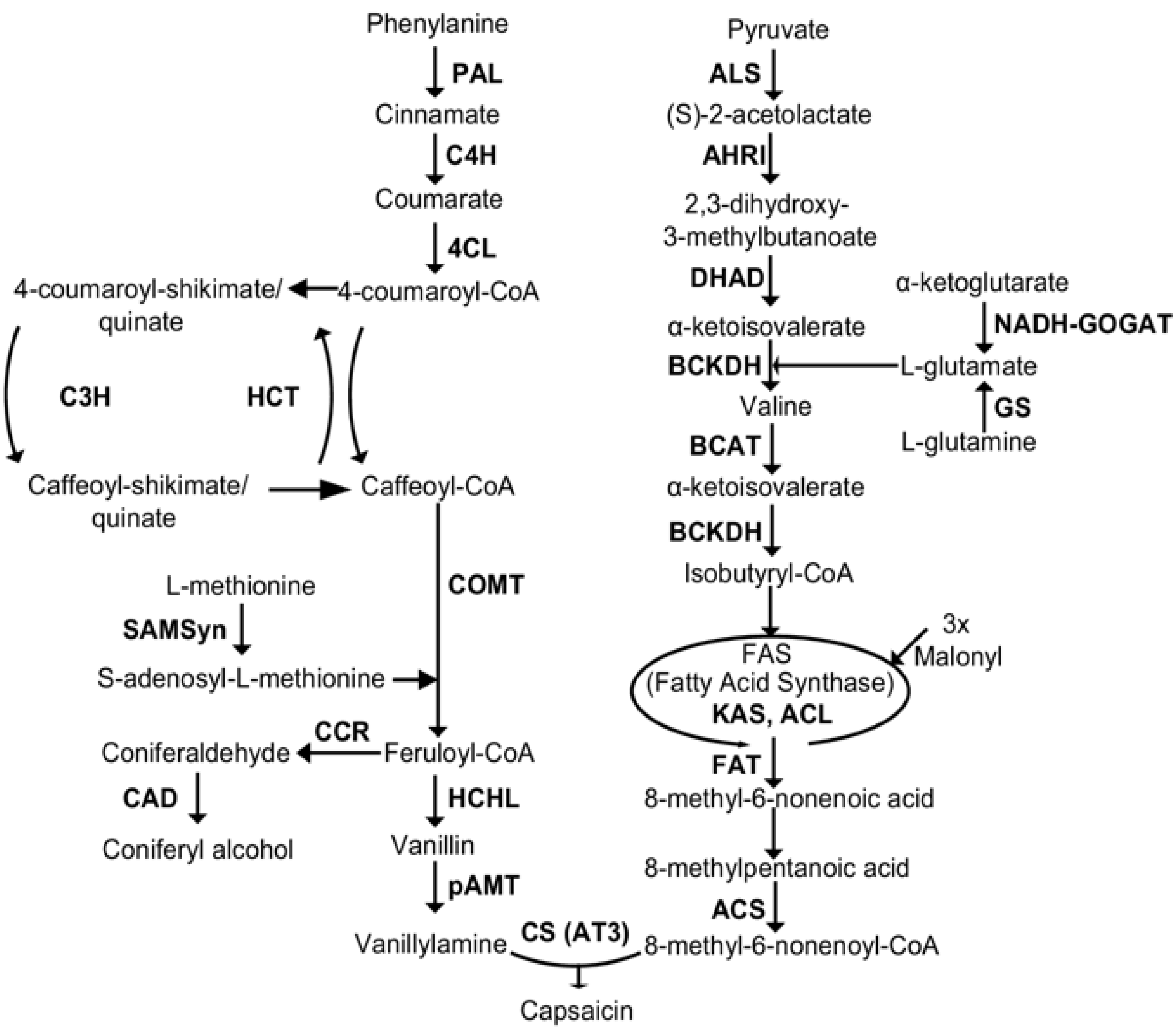


Figure 3. Model pathway of capsaicin (capsaicinoids) biosynthesis in capsicum [25]

COLORING COMPOUNDS OF CAPSICUM: Color is one of the main quality indicators for both fresh pepper fruit, as well as the food products derived from it. There are a total of four genes (y, c_1, c_2, cl), and around 20 carotenoids are responsible for the color of mature and fully ripened fruit of all the species in the genus capsicum [26]. The carotenoid pigments are highly lipid-soluble terpenoids produced during the isoprenoid (or mevalonate) pathway and are mostly stored in the chromoplasts of capsicum fruit. Carotenoids normally have a 40-carbon isoprene structural backbone with the aromatic ring structures at one or both ends of the molecule, and the chemical structure of the carotenoids results from 5-carbon isoprenoid groups with an alternating double bond [27]. The carotenoids are present in varying colors including yellow, orange, and red, ultimately imparting yellow to red coloration in different varieties of Capsicum, and these carotenoids develop and change color as the fruit ripens [28].

At the beginning of the fruit ripening process, the carotenoids chlorophyll ratio present in capsicum fruit has been reported to be 32:68, resulting in chlorophyll imparting green color to the fruits [28]. The major carotenoids responsible for the red color in capsicum are capsanthin and capsorubin, while lutein is responsible for the color in green and yellow varieties. Moreover, yellow to orange color in Capsicum can be attributed to the presence of β-carotenes, cryptoxanthin, zeaxanthin, violaxanthin, antheraxanthin, and cucurbitaxanthin A. These carotenoids have been reported to play important roles in various biological and health activities as well, besides imparting color to capsicum fruit [26, 29].

Capsicum varieties are considered as natural coloring agents in the food industry for coloring of various types of processed foods such as sauces, gravies, condiments, salad dressings, baked goods, and snacks. Other than the food industry, the natural coloring potential of capsicum varieties is also gaining importance in the cosmetic and pharmaceutical industries for both color and nutraceutical functions [30]. Carotenoids have excellent antioxidant properties as well because of the presence of conjugated double bonds which give them the ability to protect cells by scavenging the ROS and formation of free radicals, and therefore, preventing against different degenerative diseases [31].

AROMA AND FLAVOR PROFILE OF CAPSICUM: The aroma is one of the most important indicators to determine the quality of capsicum and changes according to the variety, ripening stages, and storage method [32]. The characteristic aroma and flavor of fresh capsicum fruits can be attributed to the presence of volatile oils. The first aromatic compound identified in the bell pepper was 3-isobutyl-2-methoxypyrazine, an alkylmethoxypyrazine [33]. Since then, other volatile compounds have also been identified in different cultivars of red chili pepper, such as 2,3-butanedione, which has a certain caramel note, and 1-penten-3-one, also found associated with the pungent and spicy sensation of the *Capsicum* fruit, hexanal compounds, found to be responsible for herbal favor, 3-carene, a characteristic compound of red bell pepper, ocimene, (*E*)-2-hexenal, exhibiting sweetness, and octanal, imparting fruity notes [33].

The abundant aroma compounds reported in all cultivars of capsicum are esters, alcohols, aldehydes, ketones, terpenes, acids, furans, pyrazines, and sulfur compounds [32]. In a study, the volatile compounds have been evaluated in Brazilian *C. chinense* one of the dominant species-genus Capsicum. A total of 82 volatile compounds were detected on analysis and among them, 64 compounds were associated with the aroma of the capsicum. Among these 64 identified compounds, the main class was of esters (51%), followed by terpenes (17%), alkanes (13%), alcohols (9%), carotenes (7%), and fatty acids (3%) [34].

A similar study was conducted in Germany to analyze the flavor profile of the fruits of *C. baccatum* and *C. pubescens.* Upon analysis, around 200 volatile compounds were detected and among them, 150 volatile compounds were present in fruits of both species. The most abundant compounds were esters and terpenoids, and to a minor extent, nitrogenous compounds, sulfur compounds, phenol derivatives, alcohols, norcarotenoids, furans, ketones, and different hydrocarbons were present. Around 95 ester compounds, saturated esters such as 2-methyl propanoate, 2-methyl butanoate, 3-methyl butanoate, and 4-methylpentanoates, and among unsaturated esters, (*Z*)- 3-hexenyl 3-methyl butanoate, (*Z*)-3-hexenyl 4-methyl pentanoate, and 6-methyl-4-heptenyl 3-methyl butanoate were detected. Besides esters, 62 terpenoids were analyzed in volatile fractions of the said fruit and among 62 terpenoids, there were 35 non-oxygenated sesquiterpenes, 18 monoterpenoids, and 9 oxygenated sesquiterpenes [35]. The cultivars of *capsicum* with red fruits contain a high level of hydrocarbons and help in the biosynthesis of capsaicin and degradation of the carotenoids while the yellow and orange fruits are rich in ester compounds [5]

The worldwide acceptability of the capsicum is due to its flavor, aroma, and pungency. The pungency has a direct association with the level of capsaicinoids present, the greater the level of capsaicinoids that would be bound to the vanilloid receptors in the mouth, the greater will be the burning sensation produced. Among all of the flavor determining components, capsaicinoids contribute the most to the flavor perception attributed to capsicum [36]. According to another study, close to 30 volatile compounds have been identified which impart aroma in three species of *Capsicum* (*annum*, *chinense*, and *frutescens*) [37].

The fruity aroma of capsicum is also desirable for the utilization of pepper in different food items. The other major capsaicinoids are capsinoids, with a non-pungent characteristic that have an ester bond derived from vanillyl alcohol and fatty acid, and are classified as capsiate, dihydrocapsiate, and nordihydrocapsiate [38]. The consumption of capsinoids surpass the level of capsaicinoids in the body and offsets the level of pungency. Among all the cultivars of capsicum, *C. chinense* cultivars show a high level of pungency with a strong aroma profile [38].

BIOLOGICAL PROPERTIES OF CAPSICUM: The fruit of the capsicum plant has been used for centuries, both as fresh vegetables and a food additive in dried form. However, it has also found applications in traditional medicine to cure cough, toothache, sore throat, parasitic infections of the body, rheumatism, and wound healing [39]. Moreover, it is also used as a treatment to cure common problems including high cholesterol, high blood pressure, joint pains, and skin rashes, as well as a carminative, appetizer, in beverages, relief of neuropathy pain, and as a counter-irritant in the treatment of lumbago [40]. Some other research studies report that it acts as an antioxidant, immune modulator, helps in stimulating the gastrointestinal defense system, and salivary secretions, as well as intestinal, hepatic, and pancreatic secretions [41, 42]. The results of a study reported that the leaves of three cultivars; Blackcuban (BCPL), Hongjinju (HPL), and Yeokgang-hongjanggun (YHPL) of red pepper plants have high antioxidative properties [43]. The health-related studies associated with Capsicum are highlighted in Table 2.

Table 2: Health associated role of capsicum and its bio components

Health disorder	Bioactive compound	Mechanism	Reference
Anticancer	Capsaicin	• Helps to persuade cell cycle detention at G0/G1 phase	[74]
	Capsaicin Resveratrol	• Enhanced $FOXO_3a$ expression	[75]
	Capsaicin	• Altered histone acetylation	[76]
	Capsaicin	• Prevent the growth of colon cancer cells • Help to lower the formation and secretion of IL-1β, TNF-α, IL-10, IFN-γ, and IL-1ra	[77]
	Capsaicin	• Help to induce the secretion of IFN-γ • Stimulate the apoptosis, and reduce the TNOX activity	[55]
	Capsaicin	• Inhibit the activation of ERK • Help to reduce the paxillin and FAK phosphorylation	[56]
	Capsaicin	• Increase the regulation of Dhh/Ptch2/Zeb2 members of the Hedgehog signaling pathway, • Help to improve CD24, VEGFA and TIMP1 and lower CD44 and ALCAM mRNA gene expressions	[78]
	Capsaicin	• Reduced the proliferation of renal carcinoma cells	[79]
Anticancer	Capsaicin Sulforaphane Resveratrol Piceatannol	• Pancreatic adenocarcinoma, highly resistant to all current anti-cancer treatments but combined actions of several BFCs • Provide specific lethal effect towards tumor cells • BFCs enhanced fibrotic response as compared to gemcitabine treatment alone. • (ROS) and apoptosis increases while the cell cycle was very slightly affected	[75]
Anti-cancer	Capsazpine	• Capsazepine is a synthetic analog of capsaicin • Show anti-proliferative effects in human prostate cancer cells • Help to reduce the multiplication of tumor cells	[10]
Cardiovascular	Dietary capsaicin	• Lowers the level of triglycerides, total cholesterol content and low-density lipoprotein • In plasma help to stimulate cholesterol 7α-hydroxylase enzyme expression to prevent cardiovascular disorders	[80]
Cardio-preventive	Dihydrocapsaicin	• Cellular cholesterol decreased • Cholesterol efflux increased when cells were treated with dihydrocapsaicin	[81]
Antidiabetic	Capsaicin	• Facilitate the full activation of TRPV1-expressing neurons hyperglycemia perspective to lower the blood glucose	[82, 83]

	Capsaicin	• Reduces mitochondrial Bcl-2 protein production • Increased cytochrome c levels to cure diabetes	[84]
	Capsaicin	• Reduced the number of store lipids and glucose • Enhance adiponectin gene expression and its receptor (AdipoR2) expression for activation • Activated hepatic AMP-activated protein kinase	[85]
Anti-obesity	Capsaicin	• Improved bone morphogenetic protein-8b and brown fat specific thermos-genic uncoupling protein-1 expression to reduce obesity • Triggered browning of white adipose tissue	[86]
	Capsaicin	• Repressed initiation of adipocytic differentiation, lipogenesis, and maturation • Repressed PPARγ, C/EBPα, FABP4, and SCD-1 gene expression	[87]
	Capsaicin	• Inhibited fat accumulation and a significant decrease in HMGCoA reductase, CPT-1, FAT/CD36 and GLUT4 levels	[59]
	Capsaicin Curcumin	• Lowers the levels of malondialdehyde (aldehyde associated with lipid oxidation) and phosphatidylcholine hydro-peroxide levels • Enhanced the concentrations of catalase and superoxide dismutase activity	[88]
Antiaging	Capsaicin	• Decreased the KA-facilitated rise in cytokines IL-1β level and TNF-α declined apoptotic cell death to reduce the expression of genes	[89]
Anti-inflammatory	Dietary Capsaicin	• Reduced the production of reactive oxygen species	[80, 90]
		• Prevent the EC-LPS-induced activation of the MAPK pathway	[91]
Anti-angiogenic activity	Lipophilic antimicrobial peptides isolated from paprika leaf	• The antimicrobial peptides help to inhibit the proliferation of human umbilical vein endothelial cells • Suppressed characteristics of angiogenesis • Used for the treatment of hyper-vascularized tumors	[92].
Anti-obesity	Capsaicin	• Prevent fat accumulation in visceral and subcutaneous sites of the body • Capsaicin activates the receptor vanilloid I channel and prevent the adipogenesis • Induce apoptosis in adipocytes and pre-adipocytes to prevent adipogenesis	[93]
Memory enhancer	Green chili	• Help in the improvement of memory in exteroceptive models • Reversal of memory deficits • Enhanced scavenging of free radicals and • Inhibition of AChE enzyme • Cause a significant rise in the levels of glutathione levels in the brains	[94]
Healing of gastric ulcers	Red pepper	• Helps inhibition of acid secretion • Promote the flow of alkali and gastric mucosal secretion	[22]

Antioxidant activity of capsicum: Antioxidants have been constituents of great interest to researchers for many years now owing to their health-promoting capabilities. Their wide applications in different food items, nutraceutical products, and even cosmetics are well documented, and present an excellent prospect for food processors to extract and quantify them from different foods. Capsicum fruits are a rich source of different phytochemicals such as vitamins A and C, flavonoids, and carotenoids. According to the research studies, more than 125 volatile compounds have been identified in fresh and processed Capsicum fruits of Pakistan's bell pepper. However, their significance for aroma profile is not well reported yet [44].

The phenolic compounds tend to inhibit lipid autoxidation by acting as radical scavengers and, consequently, are essential antioxidants that protect against the propagation of oxidative stress. Research studies indicate that hotter varieties of Capsicum contain more phenolic compounds as compared to the sweeter ones [45]. There are some varieties of *C. annuum* including Jalapeño and Serrano that are considered as a good source of ascorbic acid and phenols both fresh and in their processed forms [45]. The main compounds found in the red pepper with significant antioxidant activity levels are sinapoyl and feruloyl glycosides such as trans-p-feruloyl-β-d-glucopyranoside, trans-p-sinapoyl-β-d-glucopyranoside,trans-p-ferulyl-alcohol-4-O-[6-(2-methyl-3-hydroxy-propionyl] glucopyranoside, luteolin and quercetin glycosides [46].

Antimicrobial activity of capsicum: The polyphenolic compounds present in the capsicum have exhibited excellent antimicrobial activity against both beneficial and pathogenic microbial strains. The test microorganisms used for the determination of antimicrobial sensitivity testing included standard strains of gram-positive and gram-negative bacteria *Listeria monocytogenes* ATCC 7644, *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 27853*, Proteus mirabilis* ATCC 13315, *Escherichia coli* ATCC 10536, *Salmonella enterica serovar Typhimurium* ATCC 13311, *Bacillus subtilis* ATCC 6633, *Bifidobacterium animalis* sub sp. *lactis* Bb12, *Lactobacillus acidophilus* CECT 4529, *Lactobacillus Plantarum* CECT 748, and six wild-type strains of *S. aureus* (8, 14, 26, 32, 550, 319) [47]. *C. annuum* ethanol extracts exhibited significant activity against many bacterial and fungal organisms such *as L. monocytogenes* and *Aspergillus flavus* in terms of inhibiting their growth [48].

A study by [49] reported that the methanolic extract from the red pepper was tested and found effective against the drug-resistant *Vibrio cholerae* strains. Another study reported that n-hexane and chloroform extracts from the seeds of *C. frutescens* proved highly effective against many pathogenic microbes including *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Staphylococcus aureus*, *Candida albicans*, *Candida krusei*, *Alternaria alternata* and *Aspergillus niger* [50]. In another study [51], the antimicrobial activity of the acetone and acetonitrile extracts from different parts of the *C. chinense* was reported. The results of the study indicated that both the callus and fruiting body of the *C. chinense* showed higher inhibition activity against the pathogenic *E. coli, K. pneumoniae*, *Salmonella typhi*, *S. aureus*, *Streptococcus pyogenes*, *Bacillus cereus*, *Aspergillus flavus,* and *C. albicans.* A recent study [52] investigated the antimicrobial potential of the different solvent extracts including methanol, n-hexane, n-butanol, and ethyl acetate from the leaves and fruits of the *C. annuum*.

The results indicated that the solvent extracts involving butanol and ethyl acetate from both leaves and fruits of Capsicum showed significant inhibition of growth against many pathogenic microorganisms. The growth of *E. coli* was found highly resistant to organic extracts obtained from the leaves of the plant, while *K. pneumoniae* was found highly resistant to n-hexane extract from leaves. The growth of *P. aeruginosa* and *S. aureus* was found inhibited by all the solvents from the parts of the fruit of the plant. The growth of C. albicans was effectively reduced by ethyl acetate extracted from the leaves of the capsicum.

Antitumor properties of capsicum: Capsaicin has garnered significant interest in terms of its utilization for various medical applications. It has been found effective and has exhibited protective properties against many mutagenic and tumor-causing cells, in particular, by way of inducing apoptosis in these cells. This action of capsaicin, in turn, occurs due to the activity of the tumor-associated NADH-oxidase (tNOX) enzyme which aids in enhancing the cellular growth near the plasma membranes [53]. Chili peppers are rich in β-carotenes, compounds with antimutagenic and anticarcinogenic properties. The research indicated that the genotoxic activity of urethane in yeast cells, bacteria, and mammal cells was reduced through the use of the red pepper extract. The results indicated that capsaicinoids and carotenoids exhibit considerable anti-mutagenic activity [54].

The mechanism associated with the activity of capsaicinoids is thought to be the i (ICD), a phenomenon that involves the early surface exposure to calreticulin (CRT), a multifunctional chaperone protein. During an investigation, cisplatin (a chemotherapy medication), and capsaicin compounds were found to induce ICD owing to the increased CRT expression, thereby enhancing the cell apoptosis in the human osteosarcoma cells (OCs) MG-63. The treatment with capsaicin, in particular, has been associated with the translocation of calreticulin from the intracellular surfaces to the outer cell surface, helping to increase the phagocytosis of the MG-63 cells, as well as the stimulation of interferon-gamma (IFN-γ) secretion.

This, consequently, induced apoptosis, which ultimately decreased the growth of the bladder cancer cells by way of inhibition of the activity of the tNOX enzyme, and the protein sirtuin 1 (SIRT1). Furthermore, it was discovered that capsaicin effectively lowered the expression and activity of many proteins associated with the cell cycle progression, thereby reducing the rates of proliferation and migration of the cancer cells [55, 56]. The most of the data presented in literature showed that administration of low doses of capsaicin suppress the growth of many human cancers and high doses of capsaicin to treat the cancers promotes the growth of the tumor cells [57].

Antidiabetic role of capsicum: The alkaloids present in Capsicum have proven effective in regulating the blood glucose levels, and therefore, have the potential to be used as antidiabetics for humans. A study showed that the crude extract of capsicum fruit helped in inhibiting the intestinal absorption of glucose and probably contributed to lowering the blood sugar level [4]. GDM poses a major health risk for pregnant women as well as their newborns in the future. A study was conducted in which 42 women were provided with capsaicin supplements (5 mg/day) at 22-33 gestational weeks. The results of the study indicated that chili supplements including capsaicin improved postprandial hyperglycemia and hyperinsulinemia as well as fasting lipid metabolic disorders in women with GDM, as well as significantly reducing the incidence of large-for-gestational-age (LGA) newborns [58].

Another study [59] conducted to determine the effect of DHC in mice reported positive and beneficial effects of the capsaicinoids. Apolipoprotein M (apoM), a novel lipoprotein-associated plasma protein found in the kidney and liver, is linked with the causation of diabetes mellitus and problems associated with atherosclerosis. The liver hepatocellular (HepG2) cells were treated with different concentrations of dihydrocapsaicin i.e., 0, 25, 50, and 100 μM for 24 hours and the results showed that dihydrocapsaicin efficiently reduced the apoM expression at both protein and mRNA levels in HepG2 cells in a dose- and time-dependent manner. Furthermore, the induction of dihydrocapsaicin significantly lowered atherosclerotic plaque development in $apoE^{-}/^{-}$ mice. The dihydrocapsaicin application also negatively impacted the foxhead box protein a2 (Foxa2) expression, although, had a positive effect on the liver X receptor α (LXRα) expression in HepG2 cells.

Cardiovascular role of capsicum: Capsaicinoids such as dihydrocapsaicin have also been reported to reduce the levels of plasma cholesterol, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) as well as triglycerides (TG), and inflammatory cytokines such as interleukin 1 beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). Moreover, there was a marked increase in the plasma levels of the high-density lipoprotein cholesterol (HDL-C), and Apolipoprotein A1 (apoA1). The plasma sterol analysis further confirmed the findings that capsaicinoids reduced cholesterol absorption by lowering plasma cholesterol levels. Dihydrocapsaicin, owing to its contribution to increased HDL levels, thus actively enhanced the reverse cholesterol transport (CRT) pathway, ultimately leading to suppressed atherosclerosis plaque formation, thereby also promoting cholesterol efflux in THP-1 macrophage-derived foam cells [60].

Metabolic syndrome, characterized by a coexistence of high blood glucose levels, obesity, dyslipidemia, and hypertension, is commonly regarded as a major risk factor for the development of CVDs, and consequent mortality. Various studies, both in vivo and in vitro, have been reported regarding the role of capsaicin in reducing obesity, lowering the blood glucose levels, and preventing hyperglycemic episodes, as well as blood cholesterol levels, and decreasing the incidence and prevalence of atherosclerosis. The results of the studies indicated that capsaicin exhibited an anti-hyperlipidemic effect by reducing the intestinal absorption of cholesterol. Another factor related to this effect could also be the activation of peroxisome proliferator-activated receptor α (PPARα). This beneficial anti-diabetic, antihypertensive, and anti-obesity effect attributed to capsaicins makes them ideal for their use in the treatment of metabolic syndrome and has the potential to significantly decrease the risk of mortality from cardiovascular diseases [61].

Anti-inflammatory activity of capsicum: Inflammation is a biological defense response triggered by a host of factors such as infection, injury, and toxic compounds (Chen et al., 2018), and is a pathological condition if sustained. Several studies have reported the anti-inflammatory activity of bioactive compounds sourced from *Capsicum*, including polyphenols, flavonoids, tocopherols, capsaicinoids, and capsinoids [62, 63]. The anti-inflammatory property of the capsicum is mediated by the inhibition of the (LOX). Different varieties of capsicum demonstrated varying degrees of lipoxygenase inhibition with green capsicum recording the highest (46.12%), followed by the yellow (44.09%), and the red capsicum (32.18%) varieties [64].

The anti-inflammatory properties of capsaicin's are well documented, and they are widely used in topical gel and cream formulations for pain relief. Capsaicin's release the pro-inflammatory mediators, which in turn, activate the TRPV1 (transient receptor potential cation channel subfamily V member 1, also termed as capsaicin receptors) channels associated with thermoreception and nociception, thereby inducing the inflammation response (Bujak et al., 2019; Lu et al., 2020). An investigation to evaluate the anti-inflammatory effect in murine peritoneal macrophages produced by LPS reported that capsaicin suppressed the production of prostaglandin E2 (PGE2) hormone by inhibiting the activity of the cyclooxygenase-2 (COX-2) enzyme, and the expression of inducible nitric oxide synthase (iNOS). Given that prostaglandins, COX-2, and iNOS are key pro-inflammatory mediators, the use of capsaicin ultimately contributed to a reduction in inflammation (Lu et al., 2020).

Analgesic effect of capsicum: The extracts from various species of capsicum have been investigated for analgesic effects, linking the compound with nociceptive behaviors. There is a considerable body of work in support of the findings that capsaicin can modulate analgesia by acting at the VR resulting in inhibition of substance P (SP), a neuropeptide that acts as a neurotransmitter and a neuromodulator (Davis et al., 2000). In this regard, capsaicin is particularly effective in lowering the pain associated with painful diabetic neuropathy (PDN), and herpetic and trigeminal neuralgia.

A study by reported in [64]involved the testing of the extract from *C. frutescens* and capsaicin for their effects on peripheral and central components of pain. The results indicated that capsaicin has significant analgesic effects on mechano-thermal and chemically induced pain. These results confirm the earlier findings that capsaicin is effective for the treatment of neuropathic pain from diabetes, herpes, phantom and stump pain, chronic pain from osteoarthritis, and trigeminal neuralgia.

More recently, the addition of capsaicin has proved effective as a safe topical analgesic by acting as an antiarthritic, antioxidant, and anticancer agent. Capsaicin has also exhibited antiviral properties and effectiveness for the treatment of herpes zoster infection. The Osteoarthritis Research Society International (OARSI) has recommended the topical use of capsaicin as an effective adjunctive or alternative medication to oral analgesics and anti-inflammatory drugs for the treatment of various types of pain (moderate to severe), and to reduce the inflammation in those areas of the body where traditional oral analgesics and anti-inflammatory agents generally do not respond effectively [65].

Another study reported that the carotenoid extract from the dried *C. annuum* induced significant peripheral analgesic activities at the dose values of 5, 20 ad 80 mg/kg, with the dose of 80 mg/kg registering central analgesia. The synthetic non-pungent capsaicin analogs, in particular, the N-acylvanillamides (N-AVAMs), have been studied for the determination of their anticancer and analgesic activities, and various studies have reported their anticancer action against different human cancer cell lines. A capsaicin cream (0.025%), after topical application, recorded a pain reduction of 57% and 33% in patients being treated for osteoarthritis and rheumatoid arthritis [66]. Another study conducted in rats provided conclusive evidence that a nanoemulsion of capsaicin and olive oil (in both the gel and cream formulations) proved effective when compared against a commercially available capsaicin cream both in terms of analgesic activity, as well as the side effect profile [67].

Treatment of pruritus: Chronic pruritus is a condition defined by a persistent itch lasting for more than six weeks, and can be categorized as either generalized (entire skin), or localized (restricted to a particular area, such as the scalp, back, arms, or groin). Capsicum has been found to be an effective treatment remedy for pruritus associated with psoriasis, with a study reporting that 24 hours' treatment of capsaicin was found effective in reducing the perfusion of the skin affected by lesions by 15%, as well as a reduction in (PRP) (characterized by scaling, and redness of the patients' skin), and pruritus to a varying extent [4]. Capsaicin has been shown to act by desensitizing the nerve endings, thereby reducing the conduction of cutaneous itching. Although capsaicin can impart a burning sensation after the first application, this can be overcome by increasing the concentration of *Capsicum* in the formulation [68].

UTILIZATION IN NONFOOD ITEMS: The chemical extracts from pepper horns (thick-walled chili peppers with the shape of cow horns) have been reported to be effective as an antimicrobial agent against various microorganisms. In a recent study, a nanoemulsion loaded with ethanol extract of pepper horns, and containing various bioactive components, was tested on cotton fabric for the development of medical bandages. The major constituents of the extract included 9,12-octadecadienoic (29.99%), linalyl acetate (18.38%), Z, Z-10,12-hexadecadien-1-ol acetate (14.65%), and 2-methyl-1,5-hexadiene-3-ol (3.75%). The extract demonstrated superior activity against Gram +ve bacteria and yeast, as compared to the Gram -ve bacteria. The final results also indicated that the cotton fabric treated with low capsicum-based nanoemulsion (2.5%) had the best antimicrobial properties. Moreover, these properties remained intact even after 10 washing cycles and did not have any discernible effect on the human cell lines [69].

Red chili powder and oleoresins are a rich sources of carotenoid pigments and capsaicinoids. Carotenoids and capsaicinoids which come from the enriched paprika oleoresins have proved an excellent source of color in the cosmetics and pharmaceutical industry, owing to their safety of use, and that their utilization does not require any approvals from regulatory bodies. Paprika oleoresins have found their application in bath oils as well [31]. Water-soluble bioactive compounds such as anthocyanins are also present in capsicum and are used as coloring agents in cosmetics. Furthermore, their use as therapeutic compounds (antioxidants and UV protectors) in the pharmaceutical and cosmetics industry is well documented [70]. The byproducts of Capsicum are now being used in nutricosmetics and cosmeceuticals due to their anti-oxidative and analgesic properties, in the form of oral supplements and topical applications [71, 72]. The detailed uses of capsicum and its byproducts are highlighted in Table 3.

Table 3: Past few year pieces of research on the utilization of capsicum and its products in the agro-food and cosmetic industry

Type of product	Source	Associated bioactive compound	Properties	Uses	Reference
Ground Paprika powder and oleoresins	Pungent paprika	Carotenoids and capsaicinoids	Coloring and flavoring of different food items	Agro-food industry	[95]
Paprika powder	Red sweet pepper	Carotenoids	Nitrite replacer, Help to enhance color, Prevent lipid oxidation in pork meat	Agro-food industry	[96, 97]
Paprika powder	Red sweet pepper	Carotenoids and capsaicinoids	Provide color stability in meat products, soups, sauces and snacks	Agro-food industry	[98, 99]
Paprika oleoresin	Sweet paprika, pungent paprika	Carotenoids and capsaicinoids	Help to enhance the sensory properties of food	Agro-food industry	[95, 100]
Pepper flour	Yellow pepper	Carotenoids	A major source of antioxidants, Help to enhance the proteins in wheat bread	Agro-food industry	[101]
Nanoparticle paprika oleoresin	Sweet paprika	Carotenoids	Enhancer of physical and sensory properties of cooked marinated chicken	Agro-food industry	[102]
Isopropanol pepper extraction	Chili powder	Capsaicinoids	Antimicrobial agent against *S. typhimurium* and *P. aeruginosa* in raw beef meat in combination with sodium chloride	Agro-food industry	[103]
Fractions of paprika oleoresin	Capsicum fruits	Carotenoids and capsaicinoids	Coloring and biological activities: provitamin A, antioxidant capacity, analgesic effect.	Pharmaceutical, cosmetic and agro-food industry	[104]
Encapsulation of pepper oleoresin	Chili pepper	Capsaicinoids and carotenoids	Enhancer of sensory properties (particles, emulsions) and biological activities: antimicrobial, antioxidant and anti-inflammatory	Pharmaceutical, cosmetic, and agro-food industry	[105]
Isopropanol pepper extraction	Fresh Chili pepper	Cinnamic acid, o-coumaric acid, m-coumaric acid, ferulic acid and caffeic acid	Antibacterial activity against L. Monocytogenes, B. Cereus, S. Aureus, S. Typhimurium	Pharmaceutical, cosmetic and agro-food industry	[106]

Methanol pepper extractions	Sweet pepper	Polyphenols and carotenoids	Antibacterial activity against *Bacillus cereus* and *Escherichia coli* and antifungal activities against *P. expansum* and *D. hansenii*	Pharmaceutical, cosmetic, and agro-food industry	[107]
Methanol pepper extractions	Sweet pepper	Capsidiol	Bacteriostatic properties in vitro against *Helicobacter pylori*	Pharmaceutical, cosmetic, and agro-food industry	[108]
Formulations ingredients for topical delivery	Capsicum fruit	Vitamin C and carotenoids	Antioxidant and anti-inflammatory activities, preventing skin from oxidative and UVA-mediated damage	Pharmaceutical and cosmetic industry	[71]
Pepper powder and oleoresin	Chili peppers	Capsaicin	The therapeutic agent in chronic pain syndromes and chronic inflammatory skin diseases	Pharmaceutical industry	[109, 110]
Pepper powder	Cayenne pepper	Capsaicinoids	Pharmacological activities: alter appetite sensations by higher satiation	Pharmaceutical industry	[111]

CONCLUSION AND FUTURE TRENDS: During the past few years, the popularity of different varieties of capsicum and their byproducts vehave been increasing. The Capsicum plant contains a vast variety of bioactive compounds and possesses momentous applications across a wide range of domains including food, agriculture, medicine, pharmaceuticals, and cosmetics.

Traditionally, most of the research related to capsicum was focused on the biosynthesis, and characterization of these bioactive constituents, as well as their possible extraction methods using different solvents. However, more recently, the research focus has witnessed a paradigm shift towards the aspect of the utilization of capsicum for a diverse range of applications. In compiling this review article, an attempt has been made to highlight the chemical and functional properties of capsicum.

Capsicum fruit and its associated parts are present as objects of great potential and could be utilized in many industries. The byproducts of this plant have also proven beneficial in the agro-food and textile industry. As the trend is shifting rapidly from synthetic ingredients to natural, the significance and potential of this plant are manifold. Capsicum-derived products such as chili powder, oleoresins, purified extracts, and enriched fractions are widely used due to the presence of capsaicinoids, carotenoids, and polyphenolic compounds. However, there is a need to investigate more into these bioactive components to develop more versatile and healthy food products.

Moreover, to enhance the marketing of these products, their standardization is necessary from the perspective of pungency, color, flavor, and aroma which is currently lacking. There are no harmonized guidelines in the literature for maintaining the stability, safety, and quality of capsicum-derived products, in particular, medicinal, food, and cosmetic products. Therefore, more research work is required to establish novel strategies for enhancing extraction efficiency, improving the isolation techniques of bioactive compounds, and expanding the applications of these functional components in several industries.

Competing Interest: The authors declared no conflict of interest.

Abbreviation: LPS, lipopolysaccharides; ROS, Reactive oxygen species; UV, Ultra Violet; BFC, Bioactive Food Components; LOX, Lipoxygenase enzyme; DHC, Dihydrocapsaicin; CVDs, Cardiovascular diseases; SHV, Scoville Heat Value; HVA, Homovanillic acid; ICD, Immunogenic cell death; PRP, pityriasis rubra pilaris; VR, vanilloid receptors; GDM, gestational diabetes mellitus

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