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Review

More than Heat: The Complex Nature of Pungent *Capsicum* spp.

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Abstract

For centuries, people have used herbs, plants, and spices as remedies for health problems or simply to ameliorate body energy or vitality because of the bioactive compounds they contain. The *Capsicum* genus, which includes the chili pepper, is one of the oldest crops to be domesticated and used. It is characterized by three qualities: pungency/flavor, color, and aroma. Capsaicinoids are responsible for the pungent flavor. Carotenoids and flavonoids determine the remarkable and colorful tones of chili peppers. Volatile compounds provide their characteristic aroma. This prompts consumers to purchase and utilize the numerous varieties of chili peppers, whether fresh or dried. The presence of these bioactive compounds gives chili peppers functional attributes that promote health. This paper reviews the scientific research carried out over the last 25 years on these attributes. This paper also looks at how *Capsicum* fruits could be used as a valuable source of nutrients from plants that have beneficial biological properties.

Keywords: *Capsicum* spp.; chili pepper; capsaicinoid; carotenoid; flavonoid; volatile compounds; biological activity; alkaloid; ethnopharmacology

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1. Introduction

Peppers are among the oldest cultivated crops worldwide with both sweet and hot varieties classified within the genus *Capsicum* [1–7]. The genus name *Capsicum* is thought to derive from the Greek word 'capsicon' (meaning 'to bite') or from Latin 'capsa' (the 'box') [3]. Chili peppers, chile, or simply chili are specifically meant for the spicy types [8,9]. Currently, the five domesticated spicy species are as follows: *Capsicum annuum* L., *Capsicum baccatum* L., *Capsicum chinense* Jacq., *Capsicum frutescens* L., and *Capsicum pubescens* R&P. *C. annuum* is used in both domestic and industrial processing [9].

The earliest known reference to the chili pepper was to *C. annuum*, dating back to 7000 BC. It is believed that this was consumed by the Mayans and Aztecs in Central Mexico and the Yucatan. The earliest evidence of domesticated *C. pubescens* is around 6000 years ago in Bolivia. Domesticated *C. baccatum* was identified in Perú around 2500 years ago [7]. By 1492, chili peppers had already spread across the Caribbean, Mexico, and South America. Mehta [10] pointed out that the oldest variety of chili is generally considered to be the Tepin or Chiltepin pepper (*C. annuum* var. *glabriusculum*), also known as the 'mother chilli'.

Columbus' discovery of the New World was crucial in introducing them to Europe. The varieties Columbus encountered may have been a resemblance to Habanero and the Scotch Bonnet (*C. chinensis*), which are now spread throughout the Old World. Columbus called them 'pepper' because of their similar hot taste to the European white and black spices belonging to the genus *Piper* [10]. In addition, during the 16th century, the Portuguese Vasco da Gama brought chili peppers in India and Southeast Asia, slowly replacing the local 'Pippali peppers' (or long pepper) that were hard to grow [3,10].

The culinary use of hot pepper fruits in many dishes is well known thanks to their spicy flavor and taste. However, their medicinal properties and ornamental value, which enhance human health and wellbeing, have only recently come to light in relation to their use in industrial applications. This has resulted in the significant expansion of their market around the globe.

According to FAOSTAT data [11], global chili pepper production has steadily increased, rising from 20.88 million tons in 2000 to 38.31 million tons in 2023 (Figure 1).

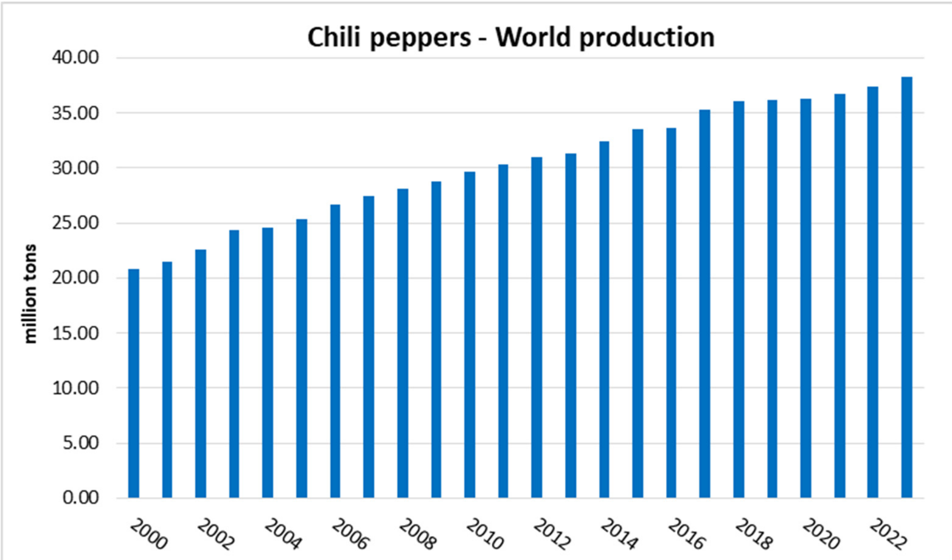

Figure 1. World chili peppers production (as million tons) from 2000 to 2023 according to FAOSTAT data [11].

The Asian region is the world's leading supplier of chili peppers, producing 25 million tons per year, which accounts for around 66% of global production. The remaining 34% of production is shared among America, Africa, Europe, and Oceania, with 5.42, 4.01, 3.49, and 0.10 million tons, respectively [11].

China is the world's largest producer of chili peppers, with an annual harvest of approximately 17.10 million tons. It is followed by Mexico, Turkey, Indonesia, Spain, and Egypt, with annual productions of 3.68, 3.08, 3.06, 1.39, and 1.07 million tons, respectively [11].

In Europe, 3.49 million tons of chili peppers were produced in 2023. Spain led the European countries in production with 1.39 million tons, followed by the Netherlands (0.42 million tons), Poland (0.29 million tons), North Macedonia (0.25 million tons), and Italy (0.23 million tons). Together, these countries accounted for 40%, 12%, 8%, 7%, and 7% of European chili pepper production, respectively, as shown in Figure 2.

The global interest in the production of hot peppers is huge. In this context, it is very important to review previous studies for creating the link between companies, breeders, and agro-food operators. This will establish existing information on the classification, description, and ethno-pharmacology of these spicy plants. The review gives a summary of all current studies about taxonomic classification, geographical distribution, botanical description and biological properties, focusing on only the five domesticated species: *C. annuum*, *C. baccatum*, *C. chinense*, *C. frutescens*, and *C. pubescens*.

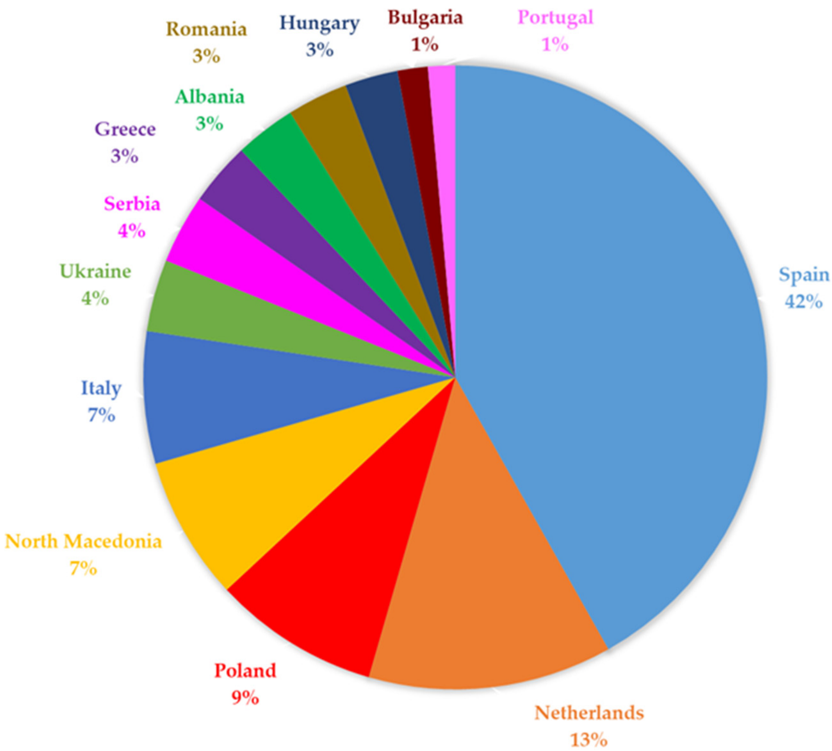

Figure 2. European chili pepper production expressed as percentage, according to FAOSTAT data of 2023 [11].

2. Review Methods

This review examines the existing literature on the health-promoting properties of *Capsicum* fruits in relation to their phytochemical content. Taxonomy, botany, geography, uses and production, and nutrition are also discussed. The *Capsicum* spp. here considered are *C. annum*, *C. baccatum*, *C. chinense*, *C. frutescens*, and *C. pubescens*.

The keywords used to search the databases were plant names (e.g., *Capsicum* spp. *C. annum*, *C. baccatum*, *C. chinense*, *C. frutescens*, and *C. pubescens*) combined with the main phytochemicals, (capsaicinoids, carotenoids, flavonoids, and volatile compounds) and biological activities (antioxidant, antimicrobial, anti-inflammatory, anti-cancer, anti-hyperglycemic, antihypertensive, anti-nociceptive, anti-neurodegenerative, anti-viral, and anti-obesity).

A broad literature examination of journals indexed in international electronical databases such as Medline, PubMed, Web of Science, Science Direct, and Scopus was conducted. Additionally, Google Books and Google Scholar were considered, too. The suitable literature cited in the review tries to cover 25 years of scientific studies on *Capsicum* spp. from 2000 to 2024 and are limited to the English language. All unpublished works, communications, case reports, and letters were excluded. Taking all this information into account, Figure 3 shows that the number of publications has gradually increased from 2000 to 2024 [12].

This study covers data from the real documentation period up to 2023, with publication of the data in 2024. The results displayed in Figure 3 are centered on the primary subject areas, including Agricultural and Biological Sciences, Biochemistry, Genetic and Molecular Biology, Pharmacology, Toxicology and Pharmaceutics, Environmental Science, Chemistry, and Medicine.

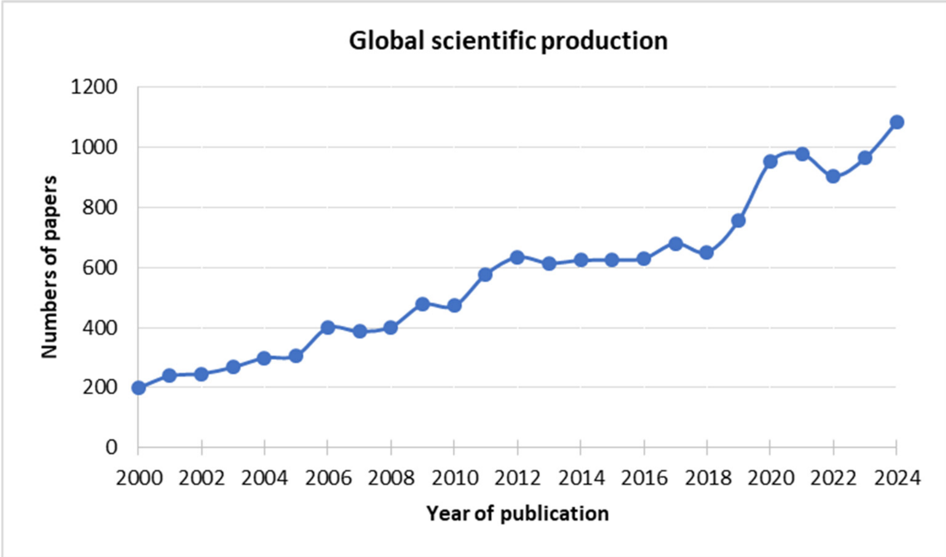

Figure 3. Global trends in scientific production on *Capsicum* [12].

3. Taxonomical Classification, Geographical, and Botanical Description

The taxonomical classification of *Capsicum* genus is given in Table 1. *Capsicum* belongs to the Solanaceae family, which comprises 90 genera and 2000 species, and is the most economically important genus in this family [1,3].

Table 1. Taxonomic classification of genus *Capsicum*.

Rank	Scientific Name
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Solanales
Family	Solanaceae
Tribe	Capsiceae
Genus	*Capsicum*

The genus *Capsicum* comprises around 40 species, 5 of which are notable for being hot (see Figure 4): *C. annuum*, *C. baccatum*, *C. chinense*, *C. frutescens*, and *C. pubescens* [2,8,13]. In the figure, the wide range of morphologies and pungency levels found in domesticated members of the *Capsicum* genus is depicted. For each species, the phenotypic traits of representative cultivars—such as fruit shape, size, and color—are shown and identified by their common names.

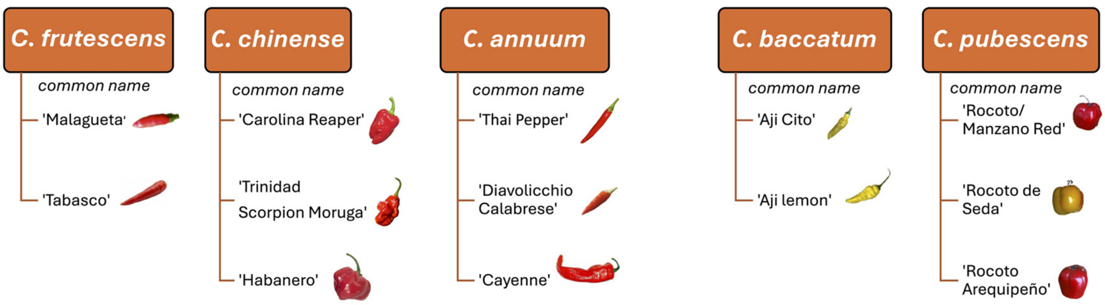

Figure 4. The five major domestic species of *Capsicum*.

The image is intended as an illustrative example and does not capture the full morphological variability within each berry type. Within each species, cultivars are arranged from top to bottom in decreasing order of pungency (measured in Scoville Heat Units, SHUs), with minor overlaps between some varieties.

Pre-Linnaean botanists proposed numerous pepper names, but in 1753, Linnaeus formalized the genus *Capsicum*, initially recognizing only *C. annuum* and *C. frutescens* and later adding *C. baccatum* (1767). Subsequent work expanded the genus to include *C. chinense* (Jacquin, 1776), and Ruiz & Pavón, in 1799, classified *C. pubescens* [13]. A confusing infraspecific system introduced by Dierbach in 1829—based on numbered fruit types without reference specimens—was later dismissed, though some of his taxa persist as synonyms. Today, *Capsicum* comprises five domesticated and twenty-six wild species, with *C. annuum* recognized as the most important cultivar due to its global distribution (China, India, Mexico, Korea, Hungary, Spain, Nigeria, Thailand, Turkey, Kenya, Sudan, Uganda, Japan, Ethiopia, Indonesia, and Pakistan) and remarkable morphological diversity [14].

Botanically, *C. annuum* has upright stems reaching up to 1 m in height, alternately arranged light- to dark-green leaves, and terminal inflorescences bearing one to five flowers. Its fruit is a pendulous or erect many-seeded berry that shows marked variability in size. *C. frutescens* (cayenne-type peppers) and *C. chinense* (habanero-type peppers) are commercially cultivated in limited regions of Central America, West and Central Africa, and Oceania [4]. In particular, *C. frutescens* is a rather woody perennial subshrub up to 1.5 m and is known as the bird pepper. Ripe fruits are small, red, and very pungent. *C. chinense* is the most cultivated and widely distributed specie in North and South America and the West Indies. Plants are up to 75 cm high, with a glabrous and short pubescent stem. The leaves are light to dark green, and the fruits are spherical to elongated, smooth, or wrinkled. Mature fruits may be red, pink, orange, yellow, or brown [13,15]. *C. baccatum* is distinguished from other species by the yellow, brown, or dark-green colorations in the inner corolla of the flowers. *C. pubescens*, known as apple chili, is a perennial herb with a height of 0.5 m, differing from other cultivated peppers by its pubescence. Plant flowers are fragrant and blue or purple rather than white or greenish. The fruits are variable in shape and are green and yellow when immature, and red, orange, or brown at late maturing [13,15].

The commercial cultivation of *C. baccatum* (aji-type peppers) and *C. pubescens* (rocoto and manzano peppers) is restricted in Central and South America and the Caribbean [3,4]. Recently, *Capsicum assamicum* has been proposed as the new domesticated specie from the Northeast of India [16]. It is closely related to *C. frutescens* and *C. chinense* but can be differentiated for its unique characteristics in the thickness of the fruit wall and the cuticle [3].

4. Ethnopharmacology and Human Food Uses

Capsicum spp. have a long history of medicinal use dating back to pre-Hispanic Aztec and Mayan practices, as documented in various codices. The most notable of these is the *Libellus de Medicinalibus Indorum Herbis* (1522), written by the indigenous healer Martín de la Cruz [17]. In the early 20th century, ethnobotanical research conducted among the Mayan people identified approximately 32 medicinal uses for *Capsicum*, including treatments for arthritis, rheumatism, stomach pain, skin irritation, and pain from dog or snake bites [7]. However, the medicinal use of *Capsicum* is not limited to Latin America. Its applications have spread globally alongside its cultivation. In the Tibetan medical tradition, *Capsicum* is referenced in the Blue Beryl text for its properties that facilitate digestion, reduce oedema, and treat hemorrhoids, parasites, and leprosy [18]. In African traditional medicine, it has been used as an antispasmodic, pulmonary disinfectant, counter-irritant, and antitussive.

Today, *Capsicum* is used topically to treat pain, neuropathy, cluster headaches, migraines, psoriasis, neuralgia, and shingles. It is also used to treat dyspepsia, appetite loss, flatulence, atherosclerosis, stroke, heart disease, and muscle tension [19]. About a quarter of the global population consumes chili peppers daily, commonly as spices or additives. They are commonly called paprika (mild), chili (hot), or cayenne (very hot) [7]. Beyond the fruit, various parts of the plant, including leaves and seeds, are used in traditional medicine and cuisine [20]. *Capsicum* leaves are edible and toxin-free, unlike some other *Solanaceae* crops. They have a mildly bitter taste and are somewhat spicy. In the Philippines, they are known as "dahonngsili" and used in dishes like soup "tinola". In Korea, they are an ingredient in fermented "kimchi", and in Japan, they are cooked into "tsukudani", a preserved side dish [20]. Chili peppers are an essential ingredient in Italian cuisine, historically used to preserve meat and add flavor to specific regional dishes. The use of chili peppers varies geographically, being more prevalent in central and southern Italy than in the north. This is particularly evident in the Calabria region, where hot peppers reign supreme in spicy cuisine and are known as "oro rosso" (red gold). They are used fresh, dried, or infused in oils. The most iconic dish is "nduja", a spreadable hot salami made with pork fat and a high concentration of chilies. Thanks to its creamy texture, it is often spread on bread or melted into pasta sauces to create an intense flavor [8,9,21]. The most widely consumed product is chili powder, which is utilized on a daily basis by approximately one third of the Italian population [10]. Moreover, in numerous cultures, including southern Italy, chili peppers are considered decorative and are thought to be sign of good fortune.

Lastly, chili seeds are predominantly used to produce essential oil. The aroma is hot and spicy and, because the scent is very strong, is generally diluted with other essential oils to create original fragrances with unique properties [20].

5. Nutritional Composition

The use of chili fruits in most cuisines and food products was due to their distinctive flavor, color, and aroma. This has led many researchers to study their nutritional content. Table 2 shows the average nutritional composition of raw chilies, according to data reported in the United States Department of Agriculture (USDA) Nutrient Database [22].

Generally, the amount and composition of nutrients and phytochemicals in *Capsicum* spp. are found to vary extremely, depending on the species, variety, stage of maturity, and part of the plant that is being considered.

Furthermore, the climatic and storage conditions, as well as the processing practices, influenced the chili peppers' nutritional array [3,4,6,23,24]. On average, chilies have a moderate energy content (40 kcal, 2% of daily value DV), provided primarily by carbohydrates (fructose), and they exhibit a low glycemic index; they contain very little protein (4% DV) as well as lipids (1% DV). As shown in Table 2, they are cholesterol-free and contain a good amount of dietary fibers. Furthermore, fruits of the genus *Capsicum* also contain several amino acids, vitamins, and minerals that are valuable for human nutrition [1,20,25].

In particular, *Capsicum* spp. provides essential and non-essential amino acids. Above all, aspartic acid and glutamic acid are the main contributors to the flavor of chili peppers, whereas tyrosine, isoleucine, leucine, valine, phenylalanine, lysine, and arginine provide a bitter taste [26]. Moreover, tryptophan (9.3% DV), threonine (7% DV), and histidine (5.9% DV) are very important for determining chili pepper nutritional quality (Table 2). While chili peppers are not a complete protein source, they contribute to the overall amino acid intake, particularly in the branched-chain amino acid group, a complex of three essential amino acids, leucine (3.8% DV), isoleucine (4.6% DV), and valine (4.6% DV), whose deficiency seems to be associated with numerous pathologies, including cancer [20].

Table 2. Average nutritional composition per 100 raw chili peppers (source: [22]).

Phytonutrient	Amount	Phytonutrient	Amount
Water	88 g	Total lipids	0.44 g
Energy	40 kcal (166 kJ)	Saturated fatty acids	0.042 g
Ash	0.87 g	Monounsaturated fatty acids	0.024 g
Carbohydrates	8.81 g	Polyunsaturated fatty acids	0.239 g
Fibers	1.5 g	Cholesterol	n.d.
Total Sugars	5.3 g	Proteins	1.87 g
Tyrosine	42 mg	Valine	84 mg
Tryptophan	26 mg	Arginine	96 mg
Threonine	74 mg	Histidine	41 mg
Isoleucine	65 mg	Alanine	82 mg
Leucine	105 mg	Aspartic acid	286 mg
Lysine	89 mg	Glutamic acid	264 mg
Methionine	24 mg	Glycine	74 mg
Cysteine	38 mg	Proline	87 mg
Phenylalanine	62 mg	Serine	80 mg
Calcium, Ca	14 mg	Sodium, Na	9 mg
Iron, Fe	1.03 mg	Zinc, Zn	0.26 mg
Magnesium, Mg	23 mg	Copper, Cu	0.129 mg
Phosphorus, P	43 mg	Manganese, Mn	0.187 mg
Potassium, K	322 mg	Selenium, Se	0.5 µg
Retinol (Vitamin A)	952 IU	Vitamin K (phylloquinone)	14 µg
Thiamine (Vitamin B1)	0.072 mg	Vitamin E (α-tocopherol)	0.69 mg
Riboflavin (Vitamin B2)	0.086 mg	Folate	23 µg
Niacin (Vitamin B3)	1.24 mg	Choline	10.9 mg
Pantothenic acid (Vitamin B5)	0.201 mg	β-carotene	534 µg
Pyridoxine (Vitamin B6)	0.506 mg	α-carotene	36 µg
Vitamin D (D2 + D3)	n.d.	Cryptoxanthin	40 µg
L-Ascorbic acid (Vitamin C)	144 mg	Lutein + zeaxanthin	709 µg

n.d. = not determined.

The vitamin contents of *Capsicum* spp. can vary depending on the variety and freshness. Generally, chilies are particularly rich in vitamins, including L-ascorbic acid (vitamin C), retinol (vitamin A), and α-tocopherol (vitamin E) and B-complex group vitamins such as a thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), and pyridoxine (vitamin B6), as listed in Table 2. It is also noteworthy that they contain high levels of carotenoids (precursors of vitamin A). On average, a serving of 100 g of chili peppers provides more than the recommended daily dose of vitamin C (90 mg/day; 160% DV), reaching about 2–4 times more vitamin C than citrus fruits [3,24]. Furthermore, chili peppers exhibit a good amount of vitamin B6 (1 mg/day; 39% DV), a value 4.3 times more than oats [3,24].

Lastly, chili peppers contain high levels of minerals, including copper (14% DV), iron (13% DV), manganese (8.1% DV), phosphorus (6.1% DV), and magnesium (5.5% DV). In addition, potassium (9.5% DV) is reported to be 2.2 times higher than that of cucumber. Finally, zinc, calcium, sodium, and selenium are present in low quantities in chili peppers (Table 2).

6. Phytochemicals in *Capsicum* spp.

The biological features linked to chili peppers are mostly a result of the high level of capsaicinoids, carotenoids, flavonoids, and volatile substances. Three major attributes—flavor (pungency), color, and aroma—are within their responsibility [1,5,6,23,27].

The color of *Capsicum* fruits is generally attributed to flavonoids and carotenoids, while their pungency is produced by the accumulation of alkaloids known as capsaicinoids [1,6,23].

Although consumers associate green peppers with no heat, Guzmán et al. [28] point out that fruit color does not predict pungency. Fruit color depends mainly on variety and ripening stage, ranging from green, yellow, or white in unripe fruit to red, dark red, brown, and almost black in ripe fruit [24].

The characteristic aroma of the *Capsicum* fruits is produced by the presence of droplets of volatile essential oils in the mesocarp, with the amount of these oils increasing as the fruit ripens [1,5,6].

6.1. Capsaicinoids

The spicy flavor and pungency of chili peppers are due to a group of biomolecules called capsaicinoids, which have an alkaloid structure and are produced exclusively in *Capsicum* spp. [29,30]. The level of pungency can vary greatly depending on many factors, such as environment, soil fertility, temperature, weather, seasonal variation, seed lineage, and water availability. Pungency is expressed in Scoville Heat Units (SHUs), which is a subjective scale based on the ratio and content of capsaicinoids [14,31]. The Scoville units of measurement express the number of times a chili extract has to be diluted into H_2O to lose its pungency [32]. According to Weiss, there are five general levels of pungency using SHUs (SHUs): non-pungent (0–700 SHUs), mildly pungent (700–3000 SHUs), moderately pungent (3000–25,000 SHUs), highly pungent (25,000–80,000 SHUs), and very highly pungent (>80,000 SHUs), as classified by Weiss [33].

The pungency, measured in SHUs, of the five domesticated species of *Capsicum* spp. is as follows: *C. chinense* is above 1,000,000 SHUs, *C. frutescens* is up to 150,000 SHUs, *C. annuum* is up to 100,000 SHUs, *C. pubescens* is up to 50,000 SHUs, and *C. baccatum* is up to 30,000 SHUs, as described by Duranova et al. [3].

The Carolina Reaper (*C. chinense*) is considered the hottest chili pepper in the world, with an average pungency of 2,200,000 SHUs. When cultivated in the Yucatan region of Mexico, this pepper rates a pungency of 3,006,330 SHUs, which is the greatest value ever recorded [34].

Among the Italian varieties of *C. annuum*, the "Sigaretta" is generally considered the spiciest Italian chili pepper, with a heat rating of 85,000 SHUs. Other typical varieties range in spiciness from 5000 SHUs for the Naso di Cane and Bacio di Satana varieties to 50,000 SHUs for the Diavolicchio Calabrese cultivar [8,9].

The synthesis of capsaicinoids predominantly occurs within the placenta of the fruit, where vanillylamine, the precursor, is present in the highest concentration [6,35,36]. These compounds are produced and accumulated in this tissue before diffusing to other compartments within the fruit and other plant organs. Over 85% of capsaicinoids are found in the placenta, reaching concentrations 10 times higher than in other organs during ripening [35,37]. The second most effective organ at accumulating capsaicinoids is the seed, which absorbs them from the neighboring placental tissue [38]. Following the concentration of capsaicinoids, there is a natural decline over time as a result of the plant's natural metabolic processes [37,39].

The general chemical structure of capsaicinoids is constituted of a vanillyl group bonded with an amide and an alkyl chain, as depicted in Figure 5 [37]. Bioactivity is mainly attributed to the vanillyl group present in the structure [40,41].

As shown in Figure 5, the molecular diversity of capsaicinoids is due to the carbon chain, which may be unsaturated and branched (e.g., capsaicin, homocapsaicin, and nornocapsaicin), saturated and branched (e.g., dihydrocapsaicin, nordihydrocapsaicin, nornordihydrocapsaicin, and homodihydrocapsaicin), or saturated and linear (e.g., nonivamide). All capsaicinoids identified in the five domesticated *Capsicum* spp. are listed in Table 3.

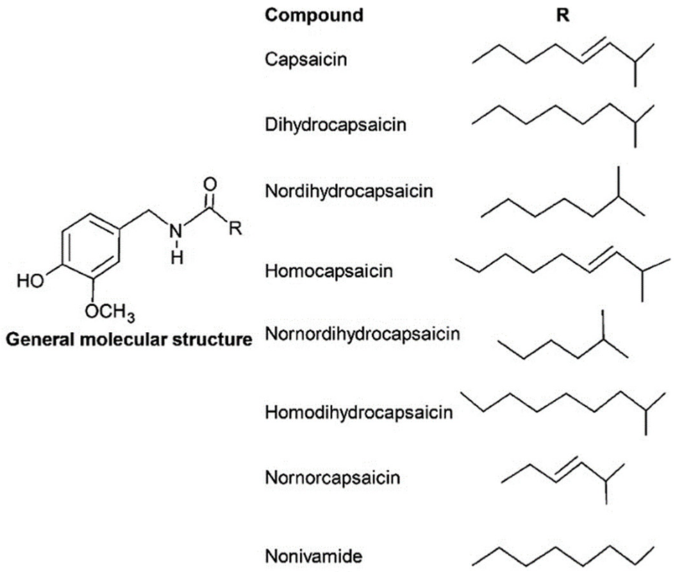

Figure 5. General molecular structure of the capsaicinoids (source: [6]).

Table 3. Main capsaicinoids present in the five species belonging to the genus *Capsicum*.

Species	Capsaicinoids	References
C. annuum	Capsaicin	[42–54]
	Homocapsaicin	[45,46,48–50]
	Dihydrocapsaicin	[42–54]
	Nordihydrocapsaicin	[42–46,48–50,53]
	Homodihydrocapsaicin	[43,46,48,49]
C. baccatum	Capsaicin	[42,43,45,47,52,55–57]
	Homocapsaicin	[45,57]
	Dihydrocapsaicin	[42–44,47,52,55,57]
	Nordihydrocapsaicin	[42,43,45,55,57]
	Nornordihydrocapsaicin	[57]
	Homodihydrocapsaicin	[43,57]
	Nonivamide	[57]
C. chinense	Capsaicin	[42,43,45,47,50,52,55,57–60]
	Homocapsaicin	[45,50,57,58]
	Dihydrocapsaicin	[42,43,45,47,50,52,55,57–60]
	Nordihydrocapsaicin	[42,43,45,50,55,57,58]
	Nornordihydrocapsaicin	[57,58]
	Homodihydrocapsaicin	[43,57,58]
	Nonivamide	[57]
C. frutescens	Capsaicin	[42,45,47,50,52,61–63]
	Homocapsaicin	[45,50,63]
	Nornorcapsaicin	[63]
	Dihydrocapsaicin	[42,45,47,50,52,61–63]
	Nordihydrocapsaicin	[42,45,47,61,63]
	Nornordihydrocapsaicin	[63]
	Homodihydrocapsaicin	[63]
	Nonivamide	[63]
C. pubescens	Capsaicin	[57,64]
	Homocapsaicin	[57]
	Dihydrocapsaicin	[57,64]
	Nordihydrocapsaicin	[57,64]
	Nornordihydrocapsaicin	[57]
	Homodihydrocapsaicin	[57]
	Nonivamide	[57]

The major capsaicinoids in *Capsicum* spp. are capsaicin and dihydrocapsaicin, which account for 89–98% of the total content in fresh fruits and are primarily responsible for about 70% of pungency [1,3,6,23,45].

Nonivamide, nornordihydrocapsaicin, homodihydrocapsaicin, nordihydrocapsaicin, and nornorcapsaicin have been described as the main minor capsaicinoids because of their relatively low abundance [49,63,65]. Nordihydrocapsaicin represents about 7% of the total capsaicinoid content, while homocapsaicin and homodihydrocapsaicin account for about 1%, both having approximately half the pungency of capsaicin. Further, nonivamide (less than 3% of the total content) is a minor capsaicinoid found in chili peppers with a pungency level similar to that of capsaicin. The concentration of these minor capsaicinoids can be used as an indicator of potential adulteration [6,37].

Researchers have detected a wide range of variation in the amount of capsaicinoids both within and between species, as shown in Table 3. Taiti et al. [43] made a comparison of the content of capsaicin, dihydrocapsaicin, nordihydrocapsaicin, and homodihydrocapsaicin in 21 different varieties belonging to three different *Capsicum* species. The varieties belonging to *C. chinense* have shown the greatest level of capsaicinoids (e.g., capsaicin 1089.3–13,630.1 mg/kg; dihydrocapsaicin 201.6–9907.3 mg/kg; nordihydrocapsaicin 14.5–1688.1 mg/kg; and homodihydrocapsaicin 17.9–824.0 mg/kg) compared to *C. baccatum*, and *C. annum*. This outcome is also confirmed by the results obtained in the study that Sora et al. performed [47], which analyzed the capsaicin and dihydrocapsaicin contents in the pulps and seeds of *C. annum* (capsaicin 7.72–61.95 mg/100 g; dihydrocapsaicin 10.02–102.70 mg/100 g), *C. baccatum* (capsaicin 2.29–10.01 mg/100 g; dihydrocapsaicin 7.58–39.47 mg/100 g), *C. chinense* (capsaicin 21.70–1024.32 mg/100 g; dihydrocapsaicin 14.15–1207.84 mg/100 g), and *C. frutescens* (capsaicin 48.27–203.84 mg/100 g; dihydrocapsaicin 68.32–410.30 mg/100 g). However, the capsaicinoid profiles do not exhibit homogeneous behavior in cultivars collected in different locations. Even when they are subject to the same conditions, a wide range of concentrations can be observed for each capsaicinoid [54].

Overall, the content of capsaicin and dihydrocapsaicin is one of the main factors that determines the commercial quality of chili peppers [43,47,52]. Depending on their intended use, breeders and consumers may require a lower or higher level of pungency and concentration of capsaicinoids. For medicinal purposes, cultivars with low to moderate capsaicinoid content are preferable in order to formulate safe medicines for human consumption [6,41]. In the food industry and for military use, however, products containing a high content of capsaicinoids are desirable, so cultivars with a moderate to high content of capsaicinoids are usually used [6,66,67]. *C. chinense* cultivars are renowned for their spiciness and typically contain higher levels of capsaicin than other species. This feature makes them more challenging to use as medicine than other species, such as *C. annuum*, which is commonly used as a spice or even as a chemical weapon [6,68]. However, alternative to capsaicinoids are the capsinoids, with promising advantages over capsaicinoids in clinical applications such as cancer prevention [69]. The main difference between the two classes is that capsinoids are less pungent than capsaicinoids [52,70]. Their molecular structure differs from that of capsaicinoids due to the presence of an ester functional group formed when the vanillyl group connects to the carbon chain. Capsinoids (capsiate, dihydrocapsiate, and nordihydrocapsiate) are synthesized almost exclusively in non-pungent cultivars of the *Capsicum* genus [52,69,70].

6.2. Carotenoids

The different colors of *Capsicum* fruits are mainly associated with the profile of some pigments (chlorophylls, anthocyanins, and carotenoids), which are all localized in the plastids of the mesocarp (the middle layer of the fruit wall). The green color of chilies is due to chlorophyll, while anthocyanins are responsible for the violet/purple pigments, and carotenoids provide the yellow-orange and red colors [3,71].

Carotenoids are the most abundant and important pigments in chili peppers due to their involvement in photosynthesis, in photo-oxidative processes (from extra UV light that is not useful for photosynthesis), and in photo-morphogenesis [71]. Moreover, they act as precursors of the growth regulator abscisic acid and attract pollinators and seed dispersal agents [71].

All carotenoids in the *Capsicum* species usually contain nine conjugated double bonds, and 95% of these pigments accumulate within chromoplasts, in fibrils, crystals, tubule structures, or in lipophilic globules [3,71].

Carotenoids normally have a 40-carbon isoprene structural backbone, with alternating double bonds and the aromatic ring structures at one or both ends of the molecule. According to their chemical structure, carotenoids can be classified into two main groups: carotenes and xanthophylls. Carotenes are linear or cyclized hydrocarbons, such as α-carotene and β-carotene, while xanthophylls include carotenoids with oxygenated functions (hydroxy, keto, methoxy, epoxy, and carbonyl groups) such as lutein, antheraxanthin, violaxanthin, cryptoxanthin, and zeaxanthin [4,6,50,71].

Considering the classification based on the chromogenic properties, carotenoids are divided into yellow-orange and red fractions. The yellow-orange fraction is composed of carotenoids with different degrees of oxidation: α-carotene, β-carotene, cryptoxanthin, lutein, zeaxanthin, antheraxanthin, and violaxanthin [4,6,23,50,71]. The red fraction differs from the yellow one due to the 3-hydroxy β rings being substituted with a 3-hydroxyacylcyclopentane ring. Examples of this fraction are capsanthin, capsorubin, neoxanthin, and cryptocapsin [71,72]. In this group, the keto-carotenoids (capsanthin and capsorubin) are found only in the *Capsicum* genus [4,6,23,71].

Red carotenoids are esterified by short-chain fatty acids such as lauric (C12:0), myristic (C14:0), and palmitic acid (C16:0). The yellow ones are esterified with myristic (C14:0), palmitic (C16:0), and linoleic acid (C18:2, Δ9–12). The number of double bonds in the fatty acid chains of yellow carotenoids makes them less stable than their red counterparts [6,71]. However, about 20% of the total carotenoids remains in their free form [6].

The main carotenoids present in *Capsicum* genus are reported in Figure 6 [4,6,50,71].

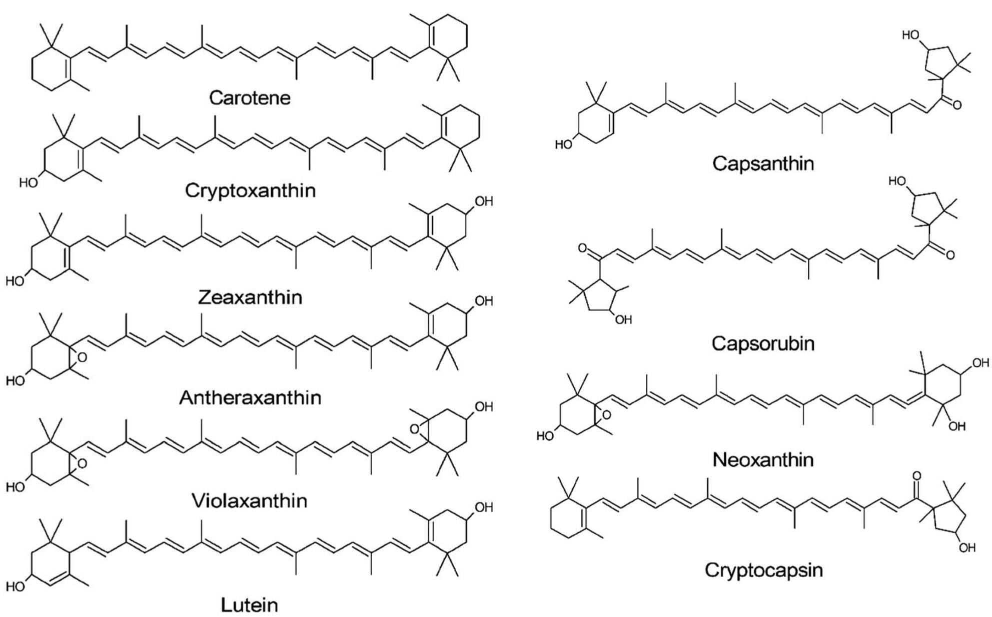

Figure 6. Principal carotenoids within the *Capsicum* genus (source: [6]).

The carotenoid profiles in chili pepper fruits are different among *Capsicum* species, depending closely on several aspects such as growing conditions, part of the plant, stage of maturity, and post-harvest management practice [3,4,6,23,73].

In pepper fruit, more than 30 different carotenoids have been identified, and in Table 4, the main carotenoids of the five domesticated species belonging to the genus *Capsicum* are reported.

Table 4. Main carotenoids present in the five species belonging to the genus *Capsicum*.

Species	Carotenoids	References	Carotenoids	References
C. annuum	Carotene	[42,50,54,74–80]	Lutein	[50,73–76,78–81]
	Cryptoxanthin	[50,54,74–78,80]	Capsanthin	[42,50,54,74,76, 78,80,82]
	Zeaxanthin	[42,50,54,74–80]	Capsorubin	[74,80–82]
	Antheraxanthin	[50,74,76,78–80]	Neoxanthin	[74,76,78–80]
	Violaxanthin	[74,76,78–80]	Cryptocapsin	[50,80]
C. baccatum	Carotene	[42,73,75,76,78]	Lutein	[73,75,76,78]
	Cryptoxanthin	[75,76,78]	Capsanthin	[42,76,78]
	Zeaxanthin	[42,75,76,78]	Capsorubin	[78]
	Antheraxanthin	[76,78]	Neoxanthin	[76,78]
	Violaxanthin	[76,78]		
C. chinense	Carotene	[42,50,73,76]	Violaxanthin	[76]
	Cryptoxanthin	[50,76]	Lutein	[50,73,75,81]
	Zeaxanthin	[42,50,75,81]	Capsanthin	[42,50,76]
	Antheraxanthin	[50,76]	Cryptocapsin	[50]
C. frutescens	Carotene	[42,50]	Violaxanthin	[83]
	Cryptoxanthin	[50]	Capsanthin	[42,50,83]
	Zeaxanthin	[42,50,83]	Capsorubin	[83]
	Antheraxanthin	[50,83]	Cryptocapsin	[50]
C. pubescens	Carotene	[78]	Lutein	[78]
	Cryptoxanthin	[78]	Capsanthin	[78]
	Zeaxanthin	[78]	Capsorubin	[78]
	Antheraxanthin	[78]	Neoxanthin	[78]
	Violaxanthin	[78]		

Generally, considering all five *Capsicum* spp., yellow-fruited cultivars presented violaxanthin and lutein as the main carotenoids (Table 4). Moreover, in species in which violaxanthin is the major carotenoid, it comprises approximately 30–50% of the total content, while when lutein is the most abundant, it can cover 41–67% [6,71]. Yellow/orange varieties are characterized by violaxanthin, lutein, and antheraxanthin, and the absence of red fraction compounds. On the other hand, the red-fruited cultivars presented capsanthin as the major carotenoid, constituting anywhere from 35 to 70% of the total carotenoid, with low levels of the yellow fraction carotenoids reported [6,71,72,78,84].

In particular, Li et al. [42] studied 75 cultivars belonging to four *Capsicum* species. In this study, the capsanthin, zeaxanthin, and β-carotene contents in *C. annum* (67 varieties), *C. baccatum* (one variety), *C. chinense* (four varieties), and *C. frutescens* (three varieties) were compared. *C. annuum* had the highest capsanthin content (170.92 µg/g), but this red carotenoid was not detected in all of them. Zeaxanthin was present in all varieties, with *C. annuum* displaying the greatest amount (118.91 µg/g). *C. annuum* also showed the maximum concentration of β-carotene (11,158.94 µg/g). Overall, no significant differences were reported in capsanthin and β-carotene among the *Capsicum* spp. ($p > 0.05$). However, the zeaxanthin content of *C. annuum* was significantly higher than that of *C. chinense* and *C. frutescens*, which did not differ significantly from each other ($p > 0.05$) [42].

Giuffrida et al. [50] also confirmed this considerable variation in carotenoid composition observed among the various cultivars. They investigated *C. annum* (three varieties), *C. chinense* (eight varieties), and *C. frutescens* (one variety) and identified 52 different carotenoids. The red color cultivars of *C. annum* and *C. chinense* showed high β-carotene content (10.8% and 4.5–19.1%, respectively), whereas some variety of *C. annum* and *C. frutescens* were characterized by high capsanthin content (3.3–7.9% and 12.6%, respectively) with no of β-carotene present. Some *C. chinense* varieties reported a high lutein amount (48.3%, 17.3%, and 15.6%), and cryptocapsin was only present in one *C. chinense* cultivar (1.5%). Moreover, a *C. chinense* variety was found to be rich in zeaxanthin (10.8%), antheraxanthin (9.9%), lutein (4.8%), and capsanthin (4.5%).

6.3. Flavonoids

Like carotenoids, flavonoids are known for their chromogenic properties and are responsible for the vivid colors observed in fruits and plants by the human eye [85,86]. Plants have been found to accumulate flavonoids, which have several functions. These include protection against UV rays, regulation of growth, the production of antimicrobial agents, and attraction to pollinators [87–90].

Flavonoids are low-molecular-weight secondary metabolites that share a common skeleton with diphenylpropanes (C6-C3-C6) and contain two phenyl rings (A and B), which are joined by a heterocyclic C ring of pyran [3,6,23,85,87–90]. They are mainly grouped into seven subclasses based on modifications to their basic skeleton: flavones, flavanols, flavanones, flavonols, isoflavones, and anthocyanins [87–91].

In chili pepper peels, flavonoids are mainly accumulated in the form of conjugated O-glycosides and C-glycosides derivates [3,6,23] and in Figure 7 are shown to be the main flavonoids detected in *Capsicum* spp.

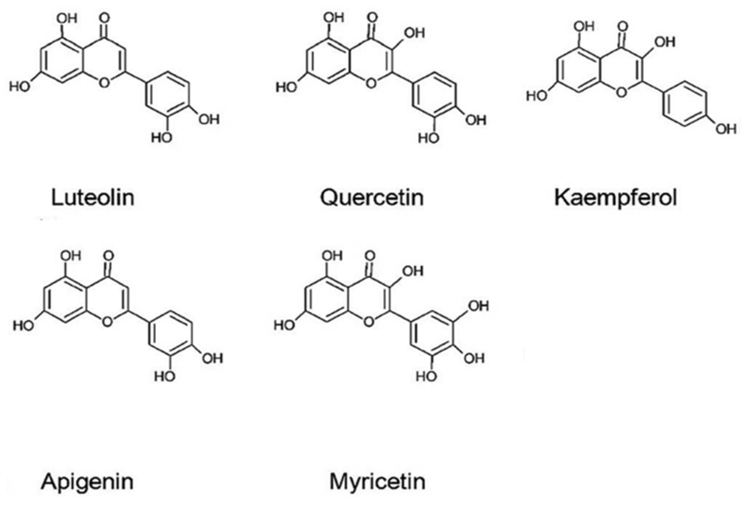

Figure 7. Chemical structure of the major flavonoids in *Capsicum* spp. (source: [6]).

According to Nascimento et al. [62], a botanical scale of chili based on the concentration of flavonoids was proposed, classifying them as low (0.1–39.9 mg/kg), moderate (40–99.9 mg/kg), and high (>100 mg/kg). They also underline the quantitative variation in flavonoids in chili peppers depending on the extraction solvent and the plant part analyzed. The study also reported that chili peppers, when compared to high-concentration plants such as wild mint and grapes, contain a moderate level of flavonoids [92].

Variations in flavonoid concentrations are primarily the result of the diversity in genotypes, landraces, and varieties, as well as in the ripening phase [59,81,86,93]. Further, differences related to analytical laboratory parameters such as sample preparation, extraction, and quantification methods also play a role [3,6]. Generally, higher levels of flavonoids have been observed in pungent peppers than in sweet ones, in green peppers than in red or orange ones, and in immature peppers than in mature ones [51,94,95]. Furthermore, the content of flavonoids exhibits a contrasting pattern compared to capsinoid and carotenoid contents. It has been reported that, as ripening progresses, flavonoid content decreases by up to 85% compared to its levels during the vegetative stages [51,95].

Table 5 lists the flavonoid compounds present in the five domesticated *Capsicum* spp., and under each flavonoid aglycone, all the related conjugated derivates are clustered (i.e., O-glycosides and C-glycosides compounds).

Table 5. Main flavonoids present in the five species belonging to the genus *Capsicum*.

Species	Flavonoids	References	Flavonoids	References
C. annuum	Apigenin	[95–100]	Kaempferol	[97,99,101,102]
	Luteolin	[81,95–102]	Myricetin	[97,102]
	Quercetin	[81,95–102]	Naringenin	[98]
C. baccatum	Apigenin	[97,99,103]	Kaempferol	[97,99,103]
	Luteolin	[97,99,103]	Myricetin	[97]
	Quercetin	[54,97,99,103]	Naringenin	[104]
C. chinense	Apigenin	[97,99]	Kaempferol	[97,99]
	Luteolin	[59,81,97,99]	Myricetin	[97]
	Quercetin	[59,81,97,99]		
C. frutescens	Apigenin	[99]	Kaempferol	[99]
	Luteolin	[62,99,102]	Myricetin	[102]
	Quercetin	[99,102]		
C. pubescens	Quercetin	[64]		

Quercetin, luteolin, and apigenin were present in major quantities in *C. annum*, *C. baccatum*, *C. chinense*, and *C. frutescens* (Table 5). Generally, these flavonoids are in their hydrolyzed form and account for more than 40% of the total flavonoid content [1,3,6,23]. In terms of their chemical structure, quercetin glycosides are only found in the O-glycosylated form and are the most abundant forms (i.e., quercetin 3-O-rhamnoside and quercetin-7-O-rhamnoside). Apigenin glycosides are identified as both C- and O-glycosides, while luteolin is exclusively present in its C-glycosylated structure [1,6,85].

In *C. chinense*, quercetin levels were reported to be 156.96 µg/g in the immature stage and 10.21 µg/g at maturity [6]. Similarly, *C. annuum* spp. exhibited 3.3 µg/g of quercetin in the immature stage and 2.7 µg/g in the ripe stage [94]. These findings indicate that quercetin is widely distributed across *Capsicum* species, though its concentration decreases markedly during fruit maturation.

Quercetin is the primary flavonoid involved in photoprotection during photosynthesis [6]. In *C. pubescens*, quercetin is the only detectable flavonoid, as reported by Meckelmann et al. [64], and no additional studies on flavonoids in this species have been published to date (Table 5). Finally, within the flavonoid group, anthocyanins have been identified in some purple or violet chili varieties, with delphinidin reported as the main compound responsible for their dark pigmentation. Overall, the exclusive detection of quercetin in *C. pubescens* suggests a more limited flavonoid profile in this species, highlighting an area where further biochemical characterization is needed. Moreover, the presence of anthocyanins in specific pigmented varieties underscores the role of flavonoids not only in photoprotection but also in determining fruit coloration, offering potential applications in breeding programs aimed at enhancing nutritional or ornamental traits.

6.4. Volatile Compounds

Capsicum spp. is among the most widely consumed spices worldwide, valued for its distinctive flavor and aroma. The perception of its complex volatile profile plays a key role in consumer acceptance and food selection [104]. Understanding this volatile composition is essential for distinguishing between species and varieties, ensuring authenticity, supporting quality control, preventing fraud, and verifying geographical origin. Moreover, the food industry increasingly seeks concentrated pepper aromas to flavor products without necessarily adding pungency [104,105].

The volatile fraction is responsible for chili pepper aromas with over 200 substances principally grouped in the following chemical classes: alkanes, alcohols, aldehydes, ketones, esters terpenes, hydrocarbons, pyrazine, and sulphur compounds [6,43,53,57,61,104–108].

A wide variety of esters and terpenes were detected in chili peppers, consistent with previous reports [43,54,57,61,104–110]. Methyl and ethyl esters contribute intense fruity aromas, while terpenes add woody, floral, fruity, and spicy notes [57,104,105,108]. Aldehydes, though generally low odor, are key to the green, pungent, and herbaceous nuances typical of *Capsicum* [57,108]. In contrast, alcohol has a higher odor threshold and therefore plays a more limited role in overall aroma. Short-chain ketones, particularly methyl ketones, provide strong aromatic notes, whereas alkanes—aliphatic, aromatic, and branched—are associated with capsaicin biosynthesis and carotenoid degradation, as reported by Pino et al. [107]. Red-fruited varieties tend to contain higher alkane levels, while orange-fruited types are richer in esters. Across *Capsicum* species, ripening typically reduces aldehyde content, yielding a more pleasant aroma in fully matured fruits. At the same time, ester formation depends on alcohol availability, which declines during ripening [104,108].

The aroma composition of *Capsicum* spp. is a complex mixture of volatile compounds that differ greatly both within and between species [6,43]. Kollsmannsberger et al. [57] found that *C. chinense* and *C. baccatum* had a high concentration and variety of esters, but *C. pubescens* had very few of these. There was also a divergence in terpenoid concentration between *C. chinense* and *C. baccatum*, with lower concentrations in the latter. Regarding terpenoids, *C. chinense* and *C. pubescens* differed in the major terpenoids (cubenene and ylangene); see Table 6.

Himachalene was mainly detected in *C. chinense* and also appeared as a distinctive component of the more pungent cultivars of *C. frutescens* and *C. annuum*, as previously reported [53,108]. Similarly, bicyclogermacrene and its derivatives—bicycloelemene and α-gurjunene—were present only in *C. chinense* and *C. pubescens* but absent in *C. baccatum*, *C. annuum*, and *C. frutescens*. In contrast, germacrene A derivatives such as β-elemene, iso-β-elemene, and 7-epi-α-selinene are typically found in certain *C. annuum* varieties [53,108] and in *C. pubescens* yet were not detected in *C. chinense* [57]. Moreover, *C. pubescens* was characterized by notably high levels of the Z and E isomers of muurola-4(14),5-diene, and cyperene was found exclusively in this species.

Among the volatile compounds, the alkyl-methoxy-pyrazines are distinctive for the *Capsicum* spp. and are not very common in other plants. These pyrazines are usually associated with a very distinct scent and contribute to creating the typical green and spicy aroma of chili peppers [107,110]. In particular, the principal pyrazine in oleoresin and paprika is tetramethyl-pyrazine [111]; 2-isobutyl-3-methoxypyrazine is involved in *C. annuum* ripening [110]; and 2-isobutyl-3-methoxypyrazine in the mature fruits of *C. chinense* [107], as reported in Table 6.

Taken together, these patterns suggest that specific sesquiterpenes and their derivatives can serve as useful chemotaxonomic markers within the *Capsicum* genus. For example, the presence of himachalene and bicyclogermacrene derivatives helps distinguish *C. chi-*

nense, while the occurrence of cyperene and abundant muurola isomers uniquely identifies *C. pubescens*. Conversely, germacrene A derivatives may be indicative of certain *C. annuum* varieties. These differences likely reflect species-specific biosynthetic pathways and may contribute to the characteristic aroma profiles and pungency levels associated with each species.

Table 6. Main volatile compounds present in the five species belonging to the genus *Capsicum*.

Species	Main Volatile Compounds	References
C. annuum	Himachalene	[53,108]
	Germacrene A (and its derivates)	[53,108]
	Tetramethyl-pyrazine	[107]
	2-isobutyl-3-methoxypyrazine	[111]
C. baccatum	Germacrene A (and its derivates)	[57]
	α-copaene	[57]
	β-elemene	[57]
C. chinense	Cubenene	[57]
	Himachalene	[57]
	Bicyclogermacrene (and its derivatives)	[108]
	2-isobutyl-3-methoxypyrazine	[107]
C. frutescens	Himachalene	[108]
C. pubescens	Ylangene	[57]
	Bicyclogermacrene (and its derivatives)	[108]
	Germacrene A (and its derivates)	[57]
	Muurola-4(14),5-diene	[57]
	Cyperene	[57]

7. Biological Activities

People have long known about the therapeutic properties of chili. Chili extracts have been shown to have a variety of uses in the production of different drugs, creams, and ointments that are applied to the skin to treat pain, migraines, headaches, psoriasis, and herpes simplex virus infections [1,3,5,6,112].

Over the last 25 years, *Capsicum* spp. has attracted increasing scientific interest due to its phytochemicals, which exhibit notable biological activity and have beneficial effects on human health and wellbeing. The use of fruits has seen a recent surge in various sectors. They have been used as spices, colorants, and preservatives to extend shelf-life and as microbial safety measures. In pharmacological and physiological fields, they have been used as tonics, antiseptics, rubefacients, stimulants, painkillers, cardiovascular protectors, anti-inflammatories, antioxidants, anti-cancer and antitumor agents. [1,3,5,6,112]. Table 7 summarizes the main bioactivities reported for *Capsicum* spp., based on preclinical evidence, conducted by means of in vitro and in vivo studies.

The most studied bioactivities reported for the five domesticated *Capsicum* spp. are antioxidant [46,51,56,60,62,64,75,77,93,94,96,99,101,114,119,124], anti-inflammatory [56,96,116–119], and antimicrobial [46,62,101,120], as reported in Table 7. Studies on other bioactivities, such as anti-hyperglycemic and antihypertensive activities, have been achieved greater importance because several chili peppers may be potentially employed as natural alternatives to help the control of diabetes and hypertension, two of the world's most severe public health problems [51,60,114,115]. Furthermore, anti-cancer, anti-neurodegenerative, anti-nociceptive, anti-obesity, and antiviral bioactivities were also described in chili peppers, as reported in Table 7 [46,60,74,82,113,119,122,123,125].

Table 7. Main bioactivities and related phytochemicals in *Capsicum* spp.

Biological Activity	Phytochemicals Group	*Capsicum* spp.	References
Anti-cancer	Capsaicinoids	*C. annum*	[46]
	Carotenoids	*C. annum*	[46,82,113]
	Flavonoids	*C. annum*	[101]
Anti-hyperglycemic	Capsaicinoids	*C. annum*	[51,114]
		C. chinense	[60]
	Carotenoids	*C. annum*	[51,115]
		C. baccatum	[115]
		C. chinense	[60,115]
		C. pubescens	[115]
	Flavonoids	*C. annum*	[51,114]
		C. chinense	[60]
Anti-hypertensive	Capsaicinoids	*C. annum*	[114]
	Carotenoids	*C. annum*	[115]
		C. baccatum	[115]
		C. chinense	[115]
		C. pubescens	[115]
	Flavonoids	*C. annum*	[114]
Anti-inflammatory	Capsaicinoids	*C. annum*	[116]
		C. baccatum	[46,117]
		C. frutescens	[118]
	Carotenoids	*C. annum*	[119]
	Flavonoids	*C. annum*	[96]
		C. baccatum	[56]
Antimicrobial	Capsaicinoids	*C. annum*	[46,120]
		C. chinense	[121]
		C. frutescens	[62]
	Carotenoids	*C. annum*	[46]
	Flavonoids	*C. annum*	[101]
		C. frutescens	[62]
	Volatile compounds	*C. chinense*	[109]
		C. frutescens	[121]
Anti-neurodegenerative	Capsaicinoids	*C. chinense*	[60]
	Carotenoids	*C. annum*	[74]
		C. chinense	[60]
	Flavonoids	*C. chinense*	[60]
Anti-nociceptive	Carotenoids	*C. annum*	[119]
Anti-obesity	Capsaicinoids	*C. annum*	[122]
	Carotenoids	*C. annum*	[123]

Table 7. *Cont.*

Biological Activity	Phytochemicals Group	*Capsicum* spp.	References
Antioxidant	Capsaicinoids	*C. annum*	[46,51,93,99,114]
		C. baccatum	[56,93,99]
		C. chinense	[60,93,99]
		C. frutescens	[62,99]
		C. pubescens	[99]
	Carotenoids	*C. annum*	[46,51,75,77,94,119]
		C. baccatum	[75]
		C. chinense	[60,75,94,124]
		C. frutescens	[94]
	Flavonoids	*C. annum*	[51,93,96,99,101,114]
		C. baccatum	[56,93,99]
		C. chinense	[60,93,94,99]
		C. frutescens	[62,94,99]
		C. pubescens	[64]
	Volatile compounds	*C. chinense*	[109]
		C. frutescens	[121]
Anti-viral	Carotenoids	*C. annum*	[125]

All these interesting and healthy biological activities are mainly attributed to the wide array of phytochemicals described in *Capsicum* spp., i.e., capsaicinoids, carotenoids, flavonoids, and volatile compounds (Table 7). In particular, the inhibition of bacteria, yeasts, and fungi is caused by capsaicinoids and phenolic compounds through an increase in the permeabilization of the membrane and cell wall. The aforementioned studies [62,120,121] collectively demonstrate that *Capsicum* components are capable of functioning in isolation or potentially synergistically with their efficacy contingent on the specific compound (capsaicinoids, phenolics, and capsinoids) and the target microbe.

Regarding capsaicinoids, they are characteristic of chili peppers and are important for their interaction with the vanilloid receptor (VR1) [126]. This is a sensorial receptor that is responsible for the neural response to temperature variations, acidosis, pain, and osmolarity. The phenomenon is characterized by the generation of sensations such as heat and/or pain, which serve as a warning signal to the body, alerting it to potential hazards. The receptor was found to be a member of the TRP family and was named TRPV1 (transient receptor potential vanilloid subtype 1). It is distributed in the brain, sensory nerves, dorsal root ganglia, bladder, gut, and blood vessels [69,126–130]. In depth, TRPV1 consists of a non-selective cation channel activated by different molecules with vanilloid functional groups, such as capsaicinoids. These biomolecules are able to activate TRPV1, producing an initial neuronal excitation tailed by a long refractory period, during which the previously excited neurons are no longer responsive to a broad range of stimuli [32,69,126]. The process is named desensitization and can be useful as a potential neuropharmacological tool in various human diseases such as in preventing chronic pain associated with arthritis, rheumatism, stiff joints, postherpetic neuralgia, diabetic neuropathy, and HIV-linked neuropathy [3,6,25,27,69]. Nevertheless, TRPV1 has much broader clinical benefits than simple pain cases, being found not only on nociceptive sensory neurons but also in a range of other tissues, including cardiovascular and gastrointestinal systems. Indeed, evidence suggests a potential for capsaicinoids to contribute to cardiometabolic protection through the activation of TRPV1, indicating that TRPV1 may represent a promising target for the management of cardiometabolic diseases, including obesity, hypertension, dyslipidemia, diabetes, and atherosclerosis [69,127,128,131].

The carotenoids present in chili peppers have been identified as highly significant antioxidants, operating in synergy with flavonoids to function as effective free radical scavengers [3,4]. The ability of carotenoids to function as free radical scavengers can be attributed to conjugated polyene systems that stabilize carotenoid radicals by delocalizing unpaired electrons across conjugated polyene chains through resonance [4].

Flavonoids, which are compounds that possess phenolic hydroxyl groups in their chemical structure, have been demonstrated to possess the capability of eliminating free radicals and ROS, in addition to exhibiting excellent metal-chelating properties. As a result, it is widely accepted that chili peppers possess a high antioxidant capacity and antiradical properties, and that they act as valuable protective agents against oxidative damage [90].

Due to the antiradical and signaling activities in the cells, protective roles of carotenoids and flavonoids from *Capsicum* spp. have been demonstrated against coronary heart disease, neurodegenerative diseases (dementia, Parkinson's, and Alzheimer's disease), stroke and some forms of cancer [4,87].

As previously described, several scientific studies have reported the numerous biological activities of *Capsicum* spp., and this effect is mainly due to the presence of capsaicinoids, carotenoids, and flavonoids. However, the volatile compounds from chili peppers are little studied in relation to their active function. Currently, Sosa-Moguel et al. [109] and Gurnani et al. [121] have been just involved in studying the biological activities of volatile fraction, both reporting antioxidant and antimicrobial properties in *C. chinense* and in *C. frutescens*, respectively (Table 7), suggesting both as new, natural, and valuable flavor with functional properties useful for food and nutraceutical products (Table 7).

8. Safety

Chili peppers are commonly used as a food seasoning due to their distinctive flavor and the characteristic sensation of pungency they provide. Capsaicin is considered safe at typical daily intake levels. It is estimated that the oral LD50 of capsaicinoids in humans is 5.0 g/kg, while the acceptable daily intake is 2.64 mg [5,68].

Traditionally, chili peppers have also been used in the cosmetic field. In particular, capsicum creams containing 0.025–0.075% capsaicin are widely available and are applied three to five times per day as topical stimulants or body creams [27]. Moreover, the efficacy of plasters containing capsicum powder or tincture has been evaluated for managing post-operative pain and nausea [132]. A high-concentration dermal patch (8% w/w capsaicin) has also been employed for HIV-related neuropathy and intractable pain [133].

Animal studies have revealed both beneficial and adverse effects of capsaicin. Notably, this pepper compound can cross the placenta and induce serious neurotoxic effects in rat fetuses [134]. In addition, exposure to capsaicinoids is known to cause bronchoconstriction, coughing, nausea, edema, skin redness, eye and nasal irritation, tearing, temporary blindness, burning sensations, and corneal lesions in rats and mice [135].

Since the 1970s, pepper spray has been used as a non-lethal defensive agent by law enforcement and private citizens worldwide [136]. Its strong irritating effect on the face is exploited to deter aggressors, control crowds, and disperse disturbances. The effects occur rapidly and include forced eyelid closure and tearing. Other reactions—such as eye burning, coughing, nasal discharge, difficulty breathing, and mouth irritation—can develop within seconds of exposure [66]. These symptoms typically last about 15 min, and full recovery usually occurs within a few hours. However, severe ocular injuries have been documented when pepper spray is applied directly to the eye using high-pressure aerosol jets [137]. Indoor use is also hazardous, as the aerosol can displace breathable air and lead to asphyxiation. Several authors have reported permanent injuries associated with the improper use of pepper sprays, particularly corneal damage, followed by cases of pulmonary injury [138,139].

The most widespread application of chili pepper extracts is as irritant agents, with oleoresin capsicum being the most commonly used [140]. This viscous extract, obtained from hot pepper fruits, contains more than a hundred different lipophilic molecules [67]. More recently, a new preparation with improved, more homogeneous, and better-defined composition has been developed as an alternative to oleoresin [141].

9. Final Considerations

The chili pepper is one of the oldest, most popular, and economically valuable preservative, natural coloring, and flavoring agent, that nowadays riches a global production of almost 40 million tons/year.

The genus *Capsicum*, with the five domesticated species *C. annuum*, *C. baccatum*, *C. chinense*, *C. frutescens*, and *C. pubescens*, is one of the most important horticultural products and an essential ingredient in all worldwide diets and cuisine. *Capsicum* spp. has been shown to be a reliable source of carbohydrates, dietary fiber, proteins, lipids, vitamins, and minerals. Chili peppers are traditionally incorporated into a wide variety of dishes and food products due to their distinctive flavor (pungency), color, and aroma.

These three distinctive quality attributes are attributed to some phytochemical compounds: Capsaicinoids are responsible for the pungent flavor of chili peppers; carotenoids and flavonoids determine the wonderful and colorful nuances of chili peppers; and volatile compounds provide their characteristic smell that encourages consumers to buy and use the numerous varieties of chili peppers, fresh or dried.

The significance of chili peppers as a component of the human diet, in addition to their relevance as a constituent in the formulation and advancement of functional foods, is intrinsically linked to the phytochemicals they contain. These phytochemicals, operating potentially in a synergistic manner, contribute to the diverse array of biological activities exhibited by *Capsicum* spp., which may offer significant benefits to human health and wellness in the pharmaceutical, medical, and cosmetics fields. In fact, antioxidant, anti-inflammatory, antihypertensive, anti-hyperglycemic, antimicrobial, and anti-cancer activities have been mainly associated in chili peppers with capsaicinoids, carotenoids, flavonoids, and volatile compound contents. Moreover, anti-neurodegenerative, anti-nociceptive, anti-viral, and anti-obesity effects have been investigated and reported.

Based on the current knowledge reviewed and summarized in this study, it is evident that *Capsicum* spp. can provide a promising and novel use in therapeutic strategies. Further efforts are necessary to exploit the huge phytochemical potential of many exotic and local species and varieties (i.e., Italian chili peppers) that, nowadays, are cultivated in smaller quantities and in limited areas of the world and, for this reason, are understudied and underutilized for research purposes. This is a stimulating challenge and extremely important strategy for the protection of *Capsicum* biodiversity that can be achieved through the adoption of measures to safeguard and/or protect these lesser-known species/varieties. So, their biochemical characterization can lead to the identification of more suitable genotypes of *Capsicum* with increased yield, disease and abiotic stress resistance, or characterized by an enhanced quality useful for the production of valuable bioactive molecules for the improvement and well-being of human life.

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