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Chapter

Capsicum Seeds as a Source of Bioactive Compounds: Biological Properties, Extraction Systems, and Industrial Application

Javier Echave, Antía G. Pereira, María Carpena, Miguel Ángel Prieto and Jesús Simal-Gandara

Abstract

Recent research has substantially focused on residual subproducts containing chemical compounds with bioactive properties. Even though there are some culinary or medicinal uses of *Capsicum* seeds, there is still a seed mass waste from pepper processing. Many pepper leading producer countries generally lack the facilities and infrastructure required for such processing technologies and so, pepper seeds are usually either destroyed or employed as landfilling or as animal feed. This involves an inadvertent economic loss for producers as well as a detrimental environmental impact. However, there is a hidden potential within the pepper processing industry related to valorization of pepper seeds to obtain added value by-products and thus reduce generated waste. Pepper seeds are a good source of antioxidants, carotenoids, phenolic acids, flavonoids, and vitamins C, E, and A and are also rich in volatile compounds, among others. The unique alkaloids of this genus are capsaicinoids and capsainoids, which have been linked to many beneficial biochemical and pharmacological effects including anti-oxidative or anti-inflammatory activities. Other prominent bioactive compounds of peppers seeds include saponins, lectins, and polyunsaturated fatty acids. In this context, an overview of the biological properties, extraction systems, and possible industrial application of bioactive compounds of pepper whole fruit and seeds is presented.

Keywords: *Capsicum* spp., seeds, extraction, bioactive, activity

1. Introduction

1.1 Characteristics of the genre

The genus *Capsicum* belongs to the Solanaceae family, which consist of different variants of peppers that can be easily recognized by their size, shape, color and degree of pungency. This latter characteristic allows the classification of chili peppers depending on their Scoville heat units (SHU), a measurement of their pungency, into spicy or hot foods (generally those with small fruits) and sweet or

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non-pungent (generally those with large fruits). This aspect is very interesting for marketing them and makes them a demanded product [1]. Considering this, we can consider for example the pungency of paprika peppers (10–30 parts per million capsaicinoids), chili peppers (30–600 parts per million) and red peppers (600–13,000 parts per million) [2]. Ripe fruits display a range of colors varying from white to deep red. Likewise, the intensity of red color and the degree of pungency are valued as major quality parameters. That is why the fruit is harvested when its red color has completely developed in order to ensure the highest quality of these features [3].

Capsicum is a very homogeneous genus with 33 species and 10 varieties (**Table 1**), with only five of them being domesticated: *Capsicum baccatum* L., *Capsicum pubescens* Ruiz & Pav., *Capsicum frutescens* L., *Capsicum chinense* Jacq. and *Capsicum. annuum* L. (**Figure 1**) native to Central and South America [5]. Each one of them was farmed independently in Pre-Columbians times in diverse regions of the American tropics [4]. They have been genetically modified to obtain varieties with agronomic interests, as in the case of *C. annuum* L. in which varieties more resistant to adverse factors were created, with a higher content and/or yield of the compounds of interest and fruit quality [6].

Amid the species *C. annuum*, there are different well know varieties like paprika, cayenne, jalapeños or chiltepin. Inside the specie *C. frutescens* are tabasco chilis; among *C. chinense*, the hottest chills (naga, habanero and Scotch bonnet) and among *C. pubescens* and *C. baccatum*, peppers emblematic from South America like rocoto or aji [7].

Although the characteristics of each species differ from each other (**Table 2**), it can be said that the genus *Capsicum* is characterized by being an annual or perennial herb or undershrub with entire or repand leaves that alternate. Its flowers are pedicelled, enclosing five petals; it is axillary and can appear solitary or in groups of two or three. Its sepals connate in a subentire or minutely five-toothed calyx that is much shorter than the fruit. It also has 5 stamens, which are adnate nearly to base of corolla-tube and are characterized for being short filaments. Its carpels connate in a two-celled (in some cases three) ovary, and its anthers are dehiscence longitudinal

Kingdom	**Plantae**
Subkingdom	Tracheobionta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Solanales
Family	Solanaceae
Genus	*Capsicum*
Species	*C. baccatum*, *C. pubescens*, *C. frutescens*, *C. chinense*, *C. annuum*
Varieties	*C. annuum* var. *annuum*, *C. annuum* var. *glabriusculum*, *C. baccatum* var. *pendulum*

Table 1.
Taxonomic classification of the genus Capsicum *[1, 4].*

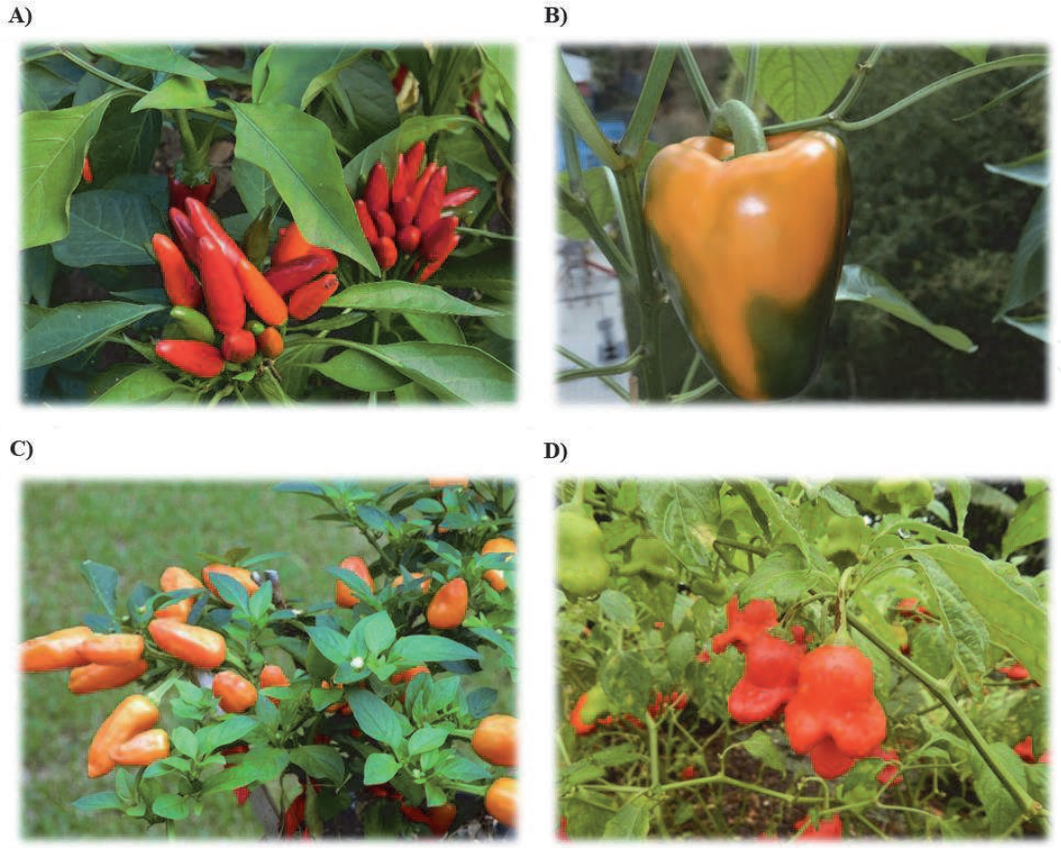


Figure 1.
Some of the major cultivated pepper species. (A) Capsicum frutescens*; (B)* Capsicum annuum*; (C)* Capsicum chinense*, and (D)* Capsicum baccatum*.*

Species	Flower color	N° flower	Seed color	Calyx constriction	Distribution
C. annuum	White	1	Tan	Absent	Colombia, USA
C. frutescens	Green	2–5	Tan	Absent	No studies
C. chinese	White-green	2–5	Tan	Present	South America
C. baccatum	White with yellow spot	1–2	Tan	Absent	South America
C. pubescens	Purple	1–2	Black	Absent	South America

Table 2.
Characteristics that allow to distinguish between the most common species of the Capsicum *genus [8].*

without any exceeding filaments. As for fruit and seeds, the first is irregularly shaped (globose or elongate) with many seeded berries. Seeds are discoid, smooth or subscabrous [8].

Thus, its physical appearance defers from one species to another. For example, *Capsicum annuum* is an annual cultivate that reaches a height of 1 m and has glabrous or pubescent lanceolate leaves, white flowers, and fruit of varying length, color, and pungency depending upon the cultivar and growth conditions. It also the most widely cultivated pepper species around the world. Considering another species, *Capsicum frutescens* is a short-lived perennial with woody stems that reach

a height of 2 m, with glabrous or pubescent leaves, with two or more greenish-white flowers per node, and extremely pungent fruit [2].

Being a cold sensitive plant, the best conditions for production are between 7 and 29°C and an annual precipitation of 0.3–4.6 mm. It grows best in well-drained, sandy or silt-loam soil and a soil pH of 4.3–8.7. Hot and dry weather is also desirable for fruit ripening [2]. To carry out its cultivation it is necessary to seed or transplant the peppers, harvesting 3 months after planting [2].

1.2 *Capsicum* seeds sources and production

Chili (a variety of *C. annuum*) is one of the first plants cultivated in Mesoamerica, existing evidence of its use for the last 9000 years. It can be used in multiple ways: fresh, dry, as a spice powder, natural dye, antioxidant, bactericide and fungicide, as a drug in the pharmaceutical industry, in the cosmetology industry or in food industry (sausage, canned meats) [9]. These characteristics made them an essential part of daily cooking in many Latin American and Asian countries, for example, curry blends in India or in many meat sausages both fresh and dehydrated in the Mediterranean region [3].

On the basis of extracts obtained from pre-ceramic in the Coxcatlan caves, it is believed that the domestication of *C. annuum* probably occurred in the northeast or central-east of Mexico, being older than the remains of corn, beans and pumpkin [1]. In fact, peppers presently represent one of the vegetables of greater economic importance just behind the tomato for several American tropical countries [10].

Of the five domesticated species of *Capsicum* spp., the largest cultivated and with higher production per hectare are *C. annuum* and *C. frutescens* [11]. As for its world production, it is estimated that it is nearby 24.9 million tons (*C. annuum*), making it the ninth most produced vegetable in the world. Likewise, it has had an annual average growth of 6.26% in the last 10 years, with Mexico being its main consumer with an annual average of 8 kg/person. Its main producers are China (60.6%), Turkey (8.4%), Mexico (7.8%), Spain (5.0%), USA (4.3%), Indonesia (3.4%), Nigeria (2.8%), Egypt (2.2%), Korea (2.0%) and Italy (1.7%) [7]. In Mexico, one of the countries with the highest production levels, there are about a hundred cultivars of hot *Capsicum* spp. with varying degrees of spiciness, size, shape and colors. Nonetheless, there are also varieties that are cultivated throughout the world. This is the case of *C. annuum* or *C. chinense* [12]. Hence, it is a product that is traded internationally. This means that a series of elements such as aflatoxins, pesticides, residuals, microbial contaminations or infections, capsaicin levels and color values are subjected to inspection. All these aspects are controlled by law in several countries (EU, USA) [8].

Pepper quality depends on their composition, which is determined by factors such as environmental cultivation conditions, variety, ripeness, and pre-harvest and post-harvest handling and preservation [13]. The degree of ripening required may be one of the most important factors in quality, but it will also depend on the destined market, since not the same degree of maturity is desired for all the possible uses. Notably, the moment of harvesting is also important for the maintenance of the quality as metabolic activity persists after harvesting [14].

1.3 Chemical composition

Regardless of the enormous consumption and production of this kind of vegetables, there is little data about the chemical composition of the different varieties (**Table 3**). However, the demand and cultivation of peppers, especially "hot" cultivars, has increased due to its flavoring and medicinal properties. Some of the latter have been described as anticancer, antioxidant and antimicrobial. Its edible and

Common name	State	Carbohydrates	Protein	Fat	Capsaicinoids	Fiber	Ash
Guajillo	D	58.00	12.89	12.43	5.97	Nd	7.52
Ancho	D	60.21	12.05	9.82	8.50	Nd	7.81
Pasado	D	66.18	12.61	5.41	9.74	Nd	7.18
Pasilla	D	60.53	12.28	13.76	11.80	Nd	5.85
Puya	D	63.76	13.25	8.11	12.13	Nd	7.82
M. Tres venas	D	61.05	13.28	9.61	14.40	Nd	7.02
Chiplote Meco	D	57.68	15.22	9.08	29.01	Nd	9.54
Jalapeno	D	63.97	14.36	4.23	58.40	Nd	7.32
Mirasol	D	58.96	14.05	7.49	58.55	Nd	9.61
Morita	D	58.91	14.12	7.60	67.32	Nd	8.59
Serrano	D	67.93	12.78	2.26	102.73	Nd	5.81
Chiplote	D	62.92	12.72	8.66	143.57	Nd	6.92
De Arbol	D	59.41	12.75	13.38	193.51	Nd	8.82
Piquin	D	62.25	13.72	11.02	368.83	Nd	7.28
Habanero	D	61.13	13.52	4.63	1312.10	Nd	7.51
Marako fana	D	35.3	11.8	11.2	Nd	27.3	5.3
Bako local	D	39.5	8.7	9.5	Nd	26.0	7.3
Oda haro	D	37.1	9.2	9.2	Nd	28.6	7.3
Arnoia red	F	6.23	0.15	0.54	Nd	1.62	0.62
Arnoia green	F	3.84	0.14	0.22	Nd	1.63	0.40
Arnoia green B	F	3.51	0.12	0.16	Nd	1.31	0.33
Hot pepper	D	Nd	21.29	23.65	Nd	38.76	4.94
Chunhamuchuk	D	Nd	15.05	29.27	Nd	48.72	3.59
Amhanegosa	D	Nd	14.66	26.70	Nd	52.10	3.28
Hanbando	D	Nd	14.08	27.84	Nd	38.43	3.49
Dachon I	D	Nd	15.99	19.53	Nd	50.61	3.76
Samgang	D	Nd	13.90	23.50	Nd	50.71	3.71
Chunhajeil	D	Nd	14.67	21.87	Nd	52.54	3.46
Daejangbu	D	Nd	14.88	26.50	Nd	53.78	3.47
Hongjangkun	D	Nd	15.17	21.61	Nd	54.66	3.33
Kumbit	D	Nd	15.09	23.28	Nd	46.17	3.18
Dokyachungjung	D	Nd	15.75	25.13	Nd	53.36	3.86
Dangchan	D	Nd	15.36	19.99	Nd	55.63	3.46
Chohyang	D	Nd	13.25	18.05	Nd	59.13	3.77
Taesan	D	Nd	14.71	23.45	Nd	48.80	3.11
Ganggun	D	Nd	15.55	20.63	Nd	52.71	3.43
Chungsan	D	Nd	15.06	20.45	Nd	50.75	3.05
Dachon II	D	Nd	15.89	18.83	Nd	45.73	3.61
Wangdaebak	D	Nd	16.53	23.65	Nd	54.39	3.28
Chunhailpum	D	Nd	15.70	19.79	Nd	53.34	3.38

Common name	State	Carbohydrates	Protein	Fat	Capsaicinoids	Fiber	Ash
Daechan	D	Nd	13.88	20.64	Nd	54.68	3.72
Mixed	D	Nd	14.01	24.09	Nd	50.26	3.26
Sandia	D	Nd	14.95	23.07	Nd	58.34	3.22
R-Naky	D	Nd	14.36	23.57	Nd	60.19	3.57
New Mexico 6	D	Nd	14.79	21.95	Nd	60.61	3.48
LB-25	D	Nd	14.87	25.06	Nd	52.98	3.29

F, fresh; D, dried; Nd, not described.

Table 3.
Different Capsicum *spp. and their proximate chemical composition (g/100 g) [14–18].*

nutritional value is acknowledge as well, since it is rich in vitamins (A, C, B_6, E), carotenoids (β-carotene), flavonoids, oils, oleoresins and alkaloids [19]. Therefore, the compounds that can be found in this genre are carbohydrates (accounting for approximately 85% of dry weight), polyphenols (0.5% of dry weight) and important molecules such as capsaicinoids, carotenoids and vitamins [20]. Given these facts, peppers are considered a good source of most essential nutrients [14].

The capsaicinoids content, which depends on the variety and maturation stage, will determinate the pungency. *C. chinense* and *Capsicum annuum* var. *aviculare* contain larger amounts of capsaicin and dihydrocapsaicin (ratio of 2:1), while some varieties of *Capsicum annuum* var. *annuum* showed an average proportion of 1:1. These variations could be attributed to environment, genetics and extraction methodologies [15]. Even though in some cases peppers are sought to be spicy, this can also be a limitation. This is the case, for example, in obtaining dyes from this raw material in the food industry. In this case, extraction methods need to be improved to prepare non-pungent oleoresins from pungent *Capsicum* fruits. This is achieved by the selective removal of capsaicinoids which allows the exploration of a large number of pungent varieties with good oleoresin yielding [20].

Capsaicinoids are the characteristic pungent compounds of the *Capsicum* genus. They include capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin. Capsaicin is the most abundant. As an example, capsaicin constitutes together with dihydrocapsaicin approximately 90% of total capsaicinoids content of chili peppers [15].

The characteristic red color of many peppers is determined by the presence of different carotenoids. Actually, more than 50 different carotenoids can be found in this kind of material. Some of them are capsanthin, capsorubin, and cryptocapsin which give brilliant red color (ripe fruits) or β-carotene, violaxanthin, zeaxanthin and β-cryptoxanthin which give yellow–orange color [3]. Nevertheless, the color will depend on the state of maturity. For example, jalapeño (*C. annuum*) has a green color, and when it is mature it presents an intense red color [7]. Therefore, depending on the degree of maturity, the physicochemical parameters, flavor and mineral composition differs. For example, fat, protein, ascorbic acid (vitamin C), soluble solid content and titratable acidity will increase during ripening [14].

Using jalapeño as an example to study composition, its main component is water, then carbohydrates (5.3%), fiber (2.3%), protein (1.2%), fat (0.1%) and minerals, being the most important potassium (340 mg per 100 g of fresh product). It also has calcium (25 mg per 100 g of fresh product), magnesium (25 mg per 100 g of fresh product), sodium (7 mg per 100 g of fresh product), iron (2 mg per 100 g of fresh product) and zinc (0.3 mg per 100 g of fresh product). As for vitamins, the most important are ascorbic acid, retinol and folic acid (72, 20 and 23 mg per 100 g

of fresh product, respectively). Other vitamins that can be found in peppers are thiamine, riboflavin, niacin and pyridoxine. Moreover, jalapeños also contain important amino acids such as lysine, methionine and valine (252, 40 and 23 mg per 100 g of protein, respectively) [7].

2. *Capsicum* seeds as a source of bioactive compounds

Like many fruits and plants, peppers are an excellent nutritional source. As aforementioned, it has an abundance of minerals, vitamins, aminoacids, carotenoids as also phytochemicals like phenolic compounds or polyunsaturated fatty acids (PUFAs). Likewise, capsaicins are unique to the genus *Capsicum*, being responsible of the pungency of many pepper species. Capsaicinoids have demonstrated to induce a vast range of bioactivities, such as anti-inflammatory, anticancer analgesic, antimicrobial, hypotensive and induce lower adipogenesis or lower body temperature by isolated action or in synergy with other compounds [21–25].

Different bioactive compounds have been isolated and extracted from *Capsicum* spp. fruits and seeds and its concentrations vary among species. More information on reported compounds studied may be found in (**Table 4**).

2.1 Phenolic compounds

Phenolic compounds, also referred as phenolics, are secondary metabolites that may be found in a wide spectrum of plant species. They are synthesized as a result of adaptation to biotic and abiotic stress through the phenylpropanoid pathway playing an important role in plant development, because they act as a defensive mechanism that eases plant growth against harsh conditions [33, 34]. Based on recorded knowledge, phenolic compounds exhibit numerous potential health benefits that are already well described in scientific literature and are currently a major current focus of nutritional and pharmacological research [35, 36]. Phenolic acids and flavonoids are the main phenolic phytochemicals found in peppers. Likewise, capsaicinoids are synthetized in the same biochemical pathway and exhibit some similar properties such as antioxidative activity [34].

The yield of phenolic compounds recovered from an extraction can be very different, depending largely on the extraction method, the conservation of vegetal material and maturity state [37]. Generally, fresh raw material preserves the highest quantities of phenolic compounds [16]. Several factors contribute to yielding disparity, such as heterogeneous genotypes, growing and harvesting conditions of the samples [38]. Some of the most prominent non-capsaicinoid phenolic compounds because of their valuable health benefits are phenolic acids like gallic acid, caffeic acid, chlorogenic acid or ellagic acid (**Figure 2**). Flavones are another important group of phenolic compounds, being some of the most prominent kaempferol, quercetin, luteolin or rutin (**Figure 3**) [26]. These phenolics have demonstrated great health benefits and many of them are commercially available in purified products extracted from other plant species [39, 40]. Even so, their concentration differs among species but not much among varieties [26]. Other phenolic compounds are reviewed in the next paragraphs as in the case of some carotenoids or vitamins.

Regarding capsaicinois, they are synthesized naturally in the placenta of pepper fruits by enzymatic transformation of vanillylamine, the phenolic portion of the molecule, which confers this alkaloid its antioxidant capacity [41]. The seeds are not the primary source of capsaicinoids but they may absorb them because they are in close proximity to the placenta, which is the richest capsaicin fraction [42]. Their presence in the seed and the high concentrations they achieve, has been observed to

Species and varieties	Bioactive compounds						
	Major phenolic compounds	Vitamins	Pigments	Volatiles	PUFAs	Peptides	Ref.
C. annuum	4-Hydroxybenzoic acid, vanillic acid, caffeic acid, *p*-coumaric acid, sinapic acid, ferulic acid, ellagic acid, naringein	Nd	Nd	Nd	Nd	Nd	[26]
C. annuum	Elagic acid, gallic acid, chlorogenic acid, caffeic acid, salicylic acid, rutin	Nd	Nd	Nd	Nd	Nd	[21]
C. annuum	Caffeic acid, gallic acid, ferulic acid, rutin, capsaicin, dihydrocapsaicin	Tocopherols	Capsanthin, zeaxanthin, capsorubin, lutein, β-carotene, cryptocapsin	Nd	Linoleic, palmitic, oleic acids	Nd	[27]
C. annuum	Nd	Nd	Nd	Nd	Nd	Mannose/glucose Specific lectin	[28]
C. annuum	Nd	Ascorbic acid	Nd	Betulin, β-sitosterol	Oleic, palmitic, linoleic, elaidic acids	Nd	[29]
C. annuum	Gallic acid, caffeic acid, ferulic acid, chlorogenic acid, cathechin, epicathechin capsaicin, dihydrocapsaicin	Ascorbic acid	Nd	Nd	Nd	Nd	[30]
C. annuum var. *annuum*	Caffeic acid, cinnamic acid, coumaric acid, capsaicin, vanillin	Nd	Nd	Nd	Nd	Phenyl-alanine	[31]
C. baccatum	Tannins, flavonoids, coumarins, polyphenols	Nd	Nd	Saponins	Nd	Amino acids	[32]

Nd, not described.

Table 4.
Capsicum *seeds bioactive compounds.*

rise the riper the pepper is [43]. It is also confirmed that fresh seeds yield more capsaicin than dry seeds, which suggests that surface capsaicinoids are sensitive to heat and/or oxidation [29]. "Hot" pepper cultivars attribute their pungency to high levels of capsaicinoids whereas non-pungent or "sweet" peppers (e.g., bell pepper) have very low capsaicinoids quantities [44].

Capsinoids are other non-pungent capsaicin analogues noticeably found in *C. baccatum* var. *praetermissum* and the sweet cultivar CH-19 of *C. annuum* [45, 46].

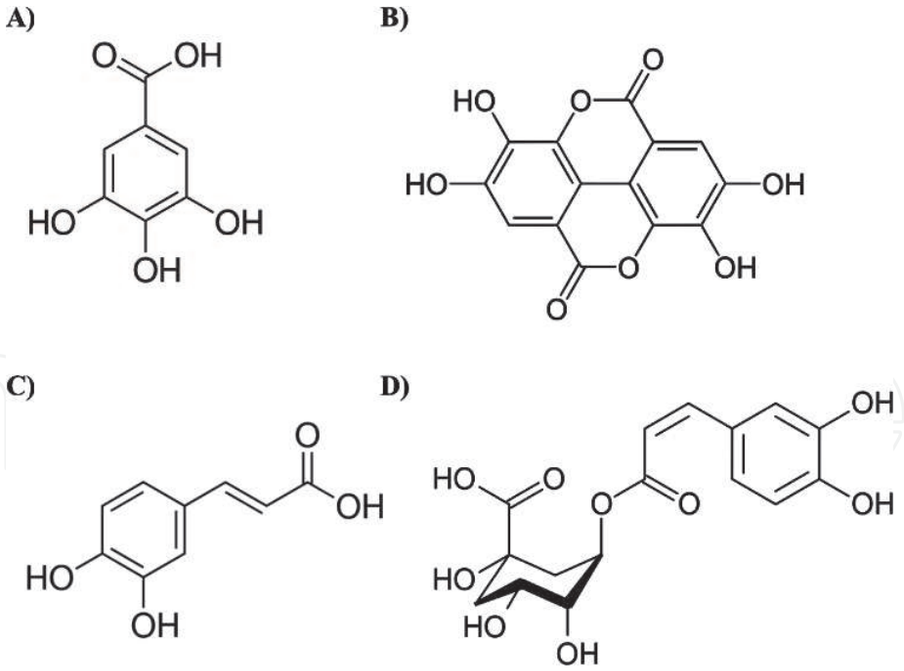


Figure 2.
Chemical structure of some main phenolic acids found in peppers: (A) gallic acid; (B) ellagic acid; (C) caffeic acid and (D) chlorogenic acid.

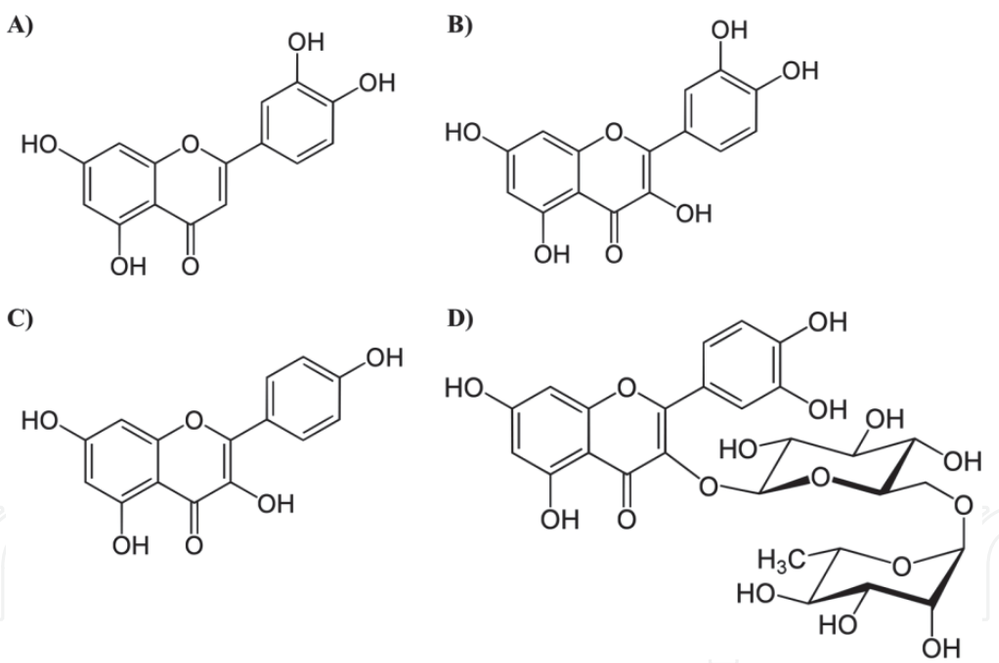


Figure 3.
Chemical structure of the main flavonoids found in pepper: (A) luteolin; (B) quercetin; (C) kaempferol; and (D) rutin.

Capsinoids exhibit biological activities similar to capsaicin due to being capsaicinoids analogs, except that they display much lower pungency in comparison [45]. Capsaicinoids and capsinoids manifest many promising therapeutic properties such as apoptosis induction, antioxidation, anticancer (cytostatic), or immunomodulation, making them attractive targets for pharmaceutical research [24, 47].

Besides, it is worth mentioning that the well-known flavone chrysoeriol (**Figure 4**), present in a multitude of vegetables and at least in *C. annuum* and *C. frutescens* fruit and seeds, has been determined to inhibit the growth of several microorganisms at very low quantities [31].

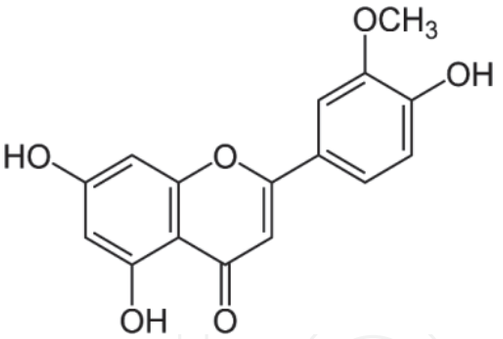


Figure 4.
Chemical structure of chrysoeriol.

2.2 Fatty acids

Peppers are fruits rich in polyunsaturated fatty acids (PUFAs), and their seeds show even greater concentration per gram [42]. The main fatty acids are indeed PUFAs [48]. These PUFAs, which are in the whole fruit and seeds, are mainly linoleic acid, palmitic acid α-linolenic acid and stearic acid [16, 48]. Moreover, peppers appear to have very low levels of saturated fatty acids. Linoleic acid has the highest concentration (≈70%) and the other fatty acids show much lower levels [48, 49]. PUFAs and specifically linoleic acid and α-linolenic acid, are recognized as essential fatty acids and are precursors of other important fatty acids in metabolism like arachidonic acid and eicosapentanoic acid or prostaglandins that in whole contribute to normal physiological performance [50].

2.3 Pigments

Chlorophylls and carotenoids constitute another group of valuable pepper nutrients that affect its color, but they also have important antioxidative, anti-inflammatory effects and promote immune response [22, 51, 52]. Zeaxanthin, β-carotene, violaxanthin, lutein and β-cryptoxanthin are the pigments with highest concentration among *Capsicum* spp. [37, 43]. Capsanthin is another red colored pigment mostly present in red bell pepper (*C. annum*) [53]. They all show strong antioxidative properties and increase their levels the more mature the pepper is [44].

β-carotene and β-cryptoxanthin for instance, possess the added value of being able to be converted to vitamin A [54]. Vitamin A plays a vital role in disease prevention and development [54].

2.4 Vitamins

As it has been mentioned, peppers contain several vitamins like ascorbic acid and tocopherols like α-tocopherol, γ-tocopherol and δ-tocopherol, are all isomers of vitamin E [55, 56]. These essential vitamins contribute to the normal metabolism, promote immune response and also have antioxidative bioactivity [52, 57]. Because of this, ascorbic acid is an essential vitamin that is also used as a natural food preserver [52]. Indeed, peppers contain levels of vitamin C corresponding with those found in many citrus fruits and other vegetables considered good sources of this vitamin [14]. Tocopherols are well-known lipophilic antioxidants and appear to exert a vital part in the normal T lymphocyte maturation, lower age-related increase in tissue inflammation and lower interleukin production [55, 58]. This makes vitamin E an important modulator to an orderly and better inflammatory reaction, among other health benefits [58].

2.5 Volatile compounds

Volatile compounds in *Capsicum* spp. have been studied because of the importance they have in many plants as pollinator attractors and their influence in odor and flavor, which are key features of any edible vegetable [59, 60]. Some of the most valuable are hexyl isopentanoate, hexyl isobutanoate, and β-ionone [61]. Extracts of *C. annuum* have also showed high levels of 4-methoxyphenol, ethylhexadecanoate, hexanal or isopulegol [62].

2.6 Other minor compounds

There are a few other minor and less studied compounds amid the different pepper species, because research has focused almost entirely on finding and studying phytochemicals of metabolic importance. In regard to these bioactive compounds, *C. annuum* or *C. frutescens* saponins have showed antimicrobial activity against several opportunistic and pathogenic fungi genres [63]. Saponins are triterpene glycosides with the ability to disrupt the cell membrane and wall of fungal cells during cell proliferation, which leads to cell lysis [27] As such, saponins do not have effect on non-germinated fungi, but they inhibit its growth. Although there are several present in pepper tissue, CAY-1 has been well-studied (**Figure 5**), presenting a high antifungal activity [60].

Another of these minor chemicals are lectins, a group of proteins with glycoside agglutination properties. Some lectins have been described in *C. frutescens* and *C. annuum* seeds and have been studied as possible antimicrobials and have yielded positive results against some fungi [28, 64].

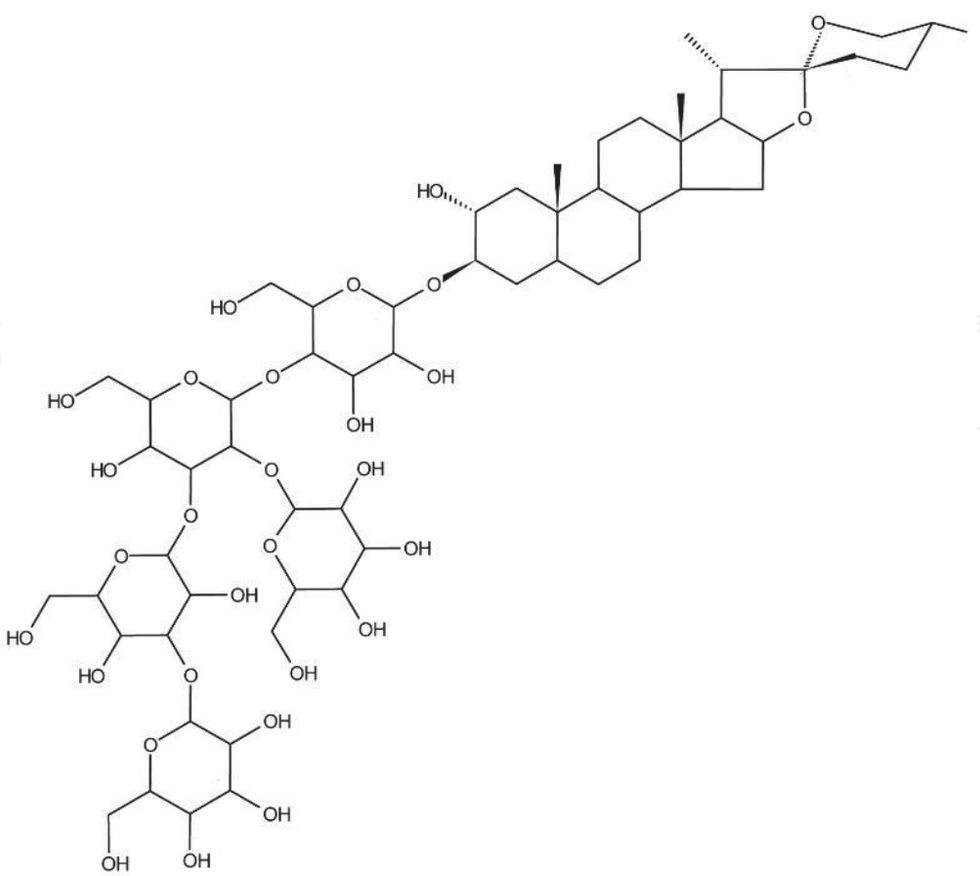


Figure 5.
Chemical structure of CAY-1. Adapted from [60].

3. Bioactivities of the raw material

In recent years, nutraceutical and therapeutic research has focused its view towards both exotic and domestic fruits and vegetables as a source of phytochemicals with the ability to induce beneficial bioactivities [65]. These natural chemicals have been and are already used as a main source of therapeutics in traditional and modern medicine, reaching one third of the total production of therapeutics [66]. Furthermore, processing waste by-products of fruits and vegetables are being researched as a viable source of phytochemicals that would be affordable and reduce economic and ecological impacts of wasted by-products or taking produce out of the food market [67, 68]. Thus, fractions that are not employed in nourishment such as the placenta, seeds or leaves of many species can prove to be a valuable resource instead of end as waste or fertilizer, which is the most common use for vegetable non-edible parts [61].

Taking into account the aforementioned compounds present in the many different species of the genus *Capsicum* and different regional cultivars, as in the case of *C. annuum*, many biological activities are expected to be found in direct or indirect physiological response to the presence of these substances. It is widely known that capasaicinoids, capsinoids, saponins, many phenolic compounds and its valuable nutrients are behind the beneficial effects of this vegetable, which has been traditionally employed as a source of medicinal remedies all across South America, Asia and Africa [63]. The intensity and type of activity may vary depending on the concentration of these compounds and will differ in each species and cultivar of *Capsicum*, the bioavailability of each compound, the ripening state and from which fraction of the vegetable the extracts are obtained [43, 44].

These bioactivities have been described in scientific reports through tissue culture and both animal and human test research as antioxidant, antimicrobial, anti-inflammatory, anticancer, analgesic or even antidiabetic [21, 22, 34]. Considering this with the fact that *Capsicum* spp. is widely grown around the world, it makes it to be considered an excellent source of new therapeutics and dietary supplements that could lead to a healthier well-being. Indeed, many extracts of pepper fruits and seeds with a varying purification degree are marketed and can be purchased [69].

Some of the most recognized bioactivities found by chemicals in the whole pepper and its seeds will be reviewed and a brief compendium of the bioactivity research can be found in **Table 5**.

3.1 Antioxidant

Oxidative stress is caused as a result of the presence of reactive oxygen species (ROS) which may be produced in oxidative metabolism and exposure to the environment [33]. The term ROS englobes the molecules superoxide radical (O_2^{2-}), the hydroxyl radical (OH^-) and hydrogen peroxide (H_2O_2). They are produced by the sequential reduction of molecular oxygen in various metabolic reactions [76]. O_2^{2-} is the most unstable form but it may dismutate to H_2O_2 by the action of endogenous superoxide dismutase (SOD) enzyme reaction or non-enzymatically [76]. The effect of oxidative stress mainly translates into changes in the rate of metabolic reduction reactions and an increased rate of DNA mutations and cell mitosis. They are also main signals indicating cell death, which in turn triggers inflammation via the pro-inflammatory factor nitric oxide (NO), which is released by macrophages [33, 76]. Since these are both cause and result of cancer development, it is considered that high levels of ROS are detrimental to health [40, 65, 76]. All living aerobic

Activity	Bioactives	Species	Type of study	Test results	Ref.
Antioxidant	Capsaicin, dihydrocapsaicin	*C. annuum*, *C. baccatum* var. *pendulum*, *C. chinense*, *C. frutescens*	In vitro	DPPH, ABTS	[68]
	Total phenolic compounds	*C. annuum*	In vitro	DPPH, ABTS, ORAC	[26]
	Phenolic extracts	*C. annuum*	In vitro	DPPH, ferrus chelating	[39]
	Seed oil	*C. annuum*	In vitro	DPPH, ABTS	[42]
Antimicrobial	Capsicosides A, G, D	*C. annuum* var. *acunimatum*	In vitro	Gia. various yeasts	[32]
	Capsaicin	*C. annuum*, *C. baccatum*, *C. chinense*, *C. frutescens*	In vitro	Gia. *Clostridium tetani* & *C. sporogenes*	[31]
	Phenolic extracts	*C. annuum*	In vitro	Gia. *S. aureus*, *L. monocytogenes*, *S. typhimurium*, *B. cereus*	[70]
	CAY-1	*C. frutescens*	In vitro	Gia. *A. flavus*, *A. fumigatus*, *A. parasiticus*, *A. niger*, *C. albicans*, *P. carinii*	[60]
	Lectins	*C. annum*	In vitro	Gia. *A. flavus*, *F. graminearum*	[28]
	Total polyphenol content, capsaicins	*C. annuum*	In vitro	Gia. *E. faecalis*, *P. aeruginosa*, *E. coli*, *S. aureus*	[21]
	Jalapeño extracts	*C. annuum* var. *annuum*	In vitro	Gia. *L. monocytogenes*	[71]
	Capsaicinoids, chrysoeriol	*C. frutescens*	In vitro	Gia *E. faecalis*, *B. subtillis*, *S. aureus*, *P. aeruginosa*, *E. coli*, *C. albicans*	[31]
	Residual aqueous extract	*C. baccatum*	In vitro	Gia *S. epidermidis*, *P. aeruginosa* biofilm	[72]
Anti-inflammatory	Capsaicin	Nd	In vitro	Inhibition of inflammatory transcription factor NF-κB and AP-1	[73]
	Capsaicin	Nd	In vitro	Inhibition of Ikα and Ikβ via NF-κB	[74]
	Capsaicin	Nd	In vitro	Inhibition of adipose tissue inflammation (interleukin 8, c-Jun)	[75]

Nd, not described; Gia., growth inhibition against; DPPH, 2,2-diphenyl-1picrylhydrazyl scavenging method; ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt scavenging methods; ORAC, oxygen radical absorbance capacity.

Table 5.
Properties and mechanisms of bioactive compounds and Capsicum *spp. extracts evaluation.*

organisms have developed defense mechanisms against oxidative stress through the synthesis of reductive biochemicals or enzymes such as SOD. The most important antioxidative biochemicals are phenolic compounds, which are prominently found

in plants [52, 66]. These antioxidants present in peppers, mainly identified as the mentioned phenolic compounds, vitamins and pigments, have the potential to reduce biological oxidative stress and thus preventing the incidence of many related diseases, but also to further food preservation by inhibiting the oxidative metabolism of decomposing fungi and bacteria [33, 35, 38]. Phenolic compounds are the principal antioxidants in nature and generally show the greatest antioxidative capacities [65]. However, high concentrations of few phenolic compounds showed pro-oxidant effects due to a concentration imbalance between ROS and the phenols, which is why it is important to maintain intake of different phenolic compounds in order to benefit from their antioxidant properties [52]. Thus, antioxidants have a wide extent of applications, and many natural and synthetic antioxidants have been used by the food industry in order to better preserve raw or precooked products that would otherwise have a much shorter shelf-life [22].

The antioxidative effect of the aforementioned phenolic compounds essentially works by scavenging free superoxide and hydroxyl radicals and thus preventing high levels of ROS, NO and oxidation of sensitive biomolecules like proteins or lipids (**Figure 6**) [36, 40]. This results in a better physiological performance, immunomodulation and DNA mutation protection. Furthermore, the decrease of oxidative stress results in better cardiovascular health. This is due to the fact that low-density lipoprotein (LDL), as the main cholesterol carrier in the circulatory system, is susceptible to oxidation by ROS [58]. Oxidized LDL presence has been found to be cause of atherosclerosis, a vascular ailment caused by the formation of plaques inside the arteries that may weaken blood flow and lead to cardiovascular diseases [77]. On top of that, pepper and its seeds are described to be one of the richest vegetables in phenolic compounds [29]. Then, it should be taken into account the antioxidant properties of the many phenolic acids, capsaicinoids, vitamins and pigments present among the *Capsicum* genus and the fact that these exploitable compounds are available not only in the fruit, but also in the non-edible fractions [39, 57, 78].

3.2 Antimicrobial

Pepper seed extracts and selected pigments, phenols, capsaicins and capsiates have been tested against the most common microorganisms present in foods and/or potential pathogens. The major antimicrobial effect of capsaicinoids has been found to be against common opportunistic and pathogenic fungi like *Fusarium* spp., *Aspergillus* spp. and yeasts like *Saccharomyces cerevisiae* or *Candida albicans*, but also against certain bacteria like *Streptococcus* spp., *Helycobacter pylori*, *Pseudomonas aeruginosa* or

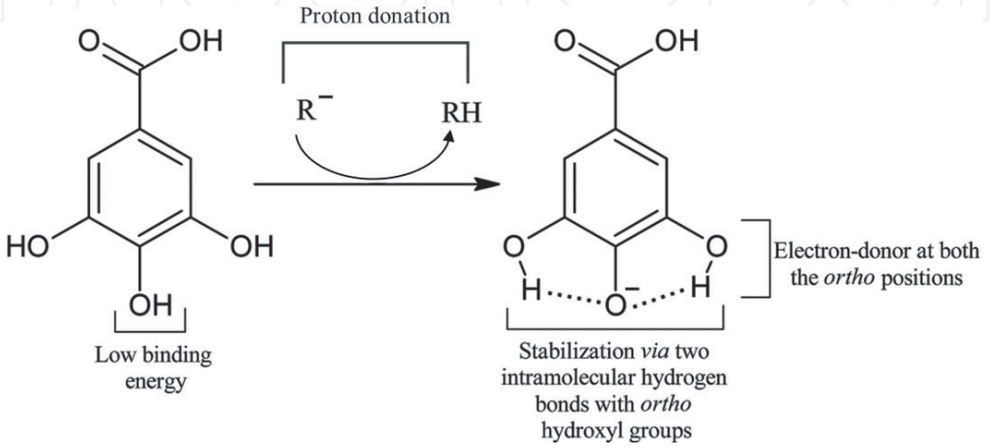


Figure 6.
Scheme of radical scavenging performed by gallic acid as an example of phenolic compounds. Adapted from [36].

Listeria monocytogenes [21, 32, 38, 79]. It has been reported that it can also reduce the virulence of pathogenic infections by *Vibrio cholerae* or *L. monocytogenes*, by inhibiting pro-inflammatory factors or toxin production [79–81]. There are few *in vivo* studies of these effects, though there are some reports of poultry showing less hepatic damage from *Salmonella enteritidis* when given feed supplemented with capsaicinoids, which could be related to its antioxidative activity [24].

Capsaicinoids appear to inhibit, fungi, and both Gram positive and negative bacterial growth in several studies. In all of them, capsaicin and/or dihydrocapsaicin showed to stop or slow colony development in a significant degree [24, 35]. Some interesting results of antimicrobial tests with capsaicinoids reported that it inhibits the growth of *Escherichia coli*, *L. monocytogenes*, *Bacillus subtillis* and many strains of *Staphylococcus aureus* [21].

Even though capsaicinoids possess these interesting antimicrobial properties, the positive correlation between antimicrobial activities, concentration and its pungency and potential irritation effects make them less suitable when it comes to applying this compound as a food preserver [46]. Thus, it is interesting to study the effects on this area of alternative chemicals found in pepper fruit and seeds. CAY-1, chrysoeriol and lectins have been previously mentioned as such.

CAY-1 is found in *C. frutescens* and a study demonstrated to produce cell membrane lysis in fungi like *Aspergillus flavus*, *Aspergillus niger*, *Fusarium solani*, *Fusarium moniliforme*, *Pneumocystis carinii* or *Cansida albicans* [60]. It is ineffective though against bacteria though, probably because of the different type of cell membrane and wall [60]. It has also been suggested to combine this saponin with certain metallic elements such as silver in order to produce antimicrobial surfactants [82]. Other saponins isolated from *C. annuum* seeds, like capsicosides, which are furostanol saponins, have showed similar effects on growth inhibition against yeasts [27].

Chrysoeriol is another potent antimicrobial compound present in a variety of plants as well as in peppers [83]. Several studies have presented that chrysoeriol is capable of greatly inhibit the growth of *Enterococcus faecalis*, *Klebsiella pneumoniae*, *S. aureus*, *L. monocytogenes*, *B. subtillis* or *C. albicans* [31, 84]. Given the very low concentrations at which it exerts its antimicrobial effect, it may be an optimal food preserver against many opportunistic and nosocomial microbes.

Certain lectins isolated from peppers have showed antifungal properties, inhibiting growth of some common opportunistic fungi like *Aspergillus flavus* and *Fusarium moniliforme* by limiting surface adherence. However, its inhibitory action is not as effective across all species of these genres [28, 85].

Furthermore, a recent study analyzed the antiadhesive capacity of natural peptides from *C. baccatum* var. *pendulum* on biofilms made by *Staphylococcus epidermidis* [64]. Considering that biofilms are a source of significant virulence, new studies on this field present extremely interesting. Altogether, these findings may contribute to develop new uses for natural antimicrobials, which would be an application of vital priority, given the global concern on the appearance of newborn antibiotic resistant microorganisms [31, 84].

3.3 Anti-inflammatory

Although an anti-inflammatory action is carried indirectly by the antioxidant capacity of other compounds to scavenge ROS and inhibit NO production, it is known that capsaicins and capsiates directly induce an anti-inflammatory effect through the activation of the transient receptor potential vanilloid 1 receptor (TRPV1) [24, 86]. TRPV1 is an ion channel receptor located in several glia that gives sensations of heat, but is also relevant in pain perception and induces this sensation,

as well as inflammation [87]. By activating this receptor, capsaicins cause the well-known pungency sensation, as well as irritation in high enough concentrations. However, after activation by capsaicinoids, the excited neurons become resistant to further stimuli [87]. Hence, after a brief burning sensation, capsaicin may act as a local analgesic in neuropathic pain [84].

Research on capsaicinoids has showed that these molecules can also decrease inflammation of adipose tissue linked to obesity [73, 75]. It seems that capsaicin is able to inhibit or at least partially decrease the production of pro-inflammatory signals like interleukin 8 (IL-8), nuclear factor kappa-light-chain-enhancer of activated B cells (NF\kappaB) or active protein 1 (AP-1) [74, 80]. This anti-inflammatory effect has the potential to make inflamed tissue less prone to tumor development as well as reduce the infection caused inflammation [25].

Still, the pungency of capsaicins poses a setback for using them without potentially hazardous secondary effects. That is why capsinoids may be a good alternative to induce similar effects to capsaicin, even though they are not found in so many pepper species [41, 45].

Although the importance of researching capsaicinoids bioactivities in pepper is due to its unique presence in this genre, the also present phenolic compounds, vitamins and pigments also bear significant anti-inflammatory properties [25, 88, 89]. Indeed, the antioxidative properties of phenolic compounds could be a key factor in reducing age-related extended tissue inflammation [25, 58]. Nonetheless, further research assessing the suitability of using as anti-inflammatory drug these phytochemicals, and specifically capsaicin, is needed.

4. Extraction systems for bioactive compounds from *Capsicum* spp.

The bioactive compounds obtained from nature are secondary metabolites produced by the organisms. The concentrations of each type of compound are very variable, so in order to have enough quantities, the development of new and advanced technologies is needed.

Although there are several extraction methodologies, there is a demand for more appropriate and standardized extraction strategies. For choosing one method over another, it must be taken into account the quantitative and qualitative characteristics of the compound of interest. In addition, to improve the efficiency of a method it is important that the nature of the source, the different parameters of the method and the possible interaction are taken into account. Experiments carried out with peppers can be seen in **Table 6**.

4.1 Conventional extraction systems

4.1.1 Maceration

Maceration (MA) is a type of solid–liquid extraction, in which the solid would be peppers. This raw material is characterized by having several compounds soluble in the liquid phase. The type of molecules extracted will depend on two factors: the type of starting material and the type of solvent used.

In order to carry out this process, the sample is suspended in the solvent at the desired temperature during the chosen time while stirring. Once the process has been carried out, the sample is centrifuged and the supernatant, which is where the compounds of interest are found, is filtered. Therefore, the process of extraction consists of two stages. On the first (washing) there is a rapid transfer of the compounds from the surface of the solid to the solvent. On the second one (transfer), the matter passes from the interior to the exterior of the solid by diffusion

Compound	Species	Extraction		Medium	Yield	Ref.
		Type	Method			
Pigments	*Capsicum* spp.	Emergent	SFE	—	6%	[90]
	C. annuum	Green	MAE	Acetone-water	—	[91]
		Emergent	SFE	—	17.4%	[92]
				—	93%	[93]
				—	7.2%	[94]
Carotenoids	*C. annuum*	Green	EAE	Viscozyme L	87%	[95]
				Pectinase	80%	[95]
				Cellulase	Low	[95]
				Viscozyme L	78%	[96]
Phenolics	*C. annuum*	Emergent	SFE	—	84%	[93]
				—	100%	[94]
Capsaicinoids	*Capsicum* spp.	Green	MAE	Acetone (30%)	0.48 mg/g	[97]
	C. annuum	Green	MAE	None	230 ppm	[98]
			UAE	None	200 ppm	[97]
				n-hexane (100%)	—	[99]
				Methanol (100%)	100%	[100]
	C. annuum	Green	EAE	Viscozyme L	88.8%	[96]
				Viscozyme L	22%	[101]
				Celluclast	20%	[101]
		Emergent	SFE	—	8.6%	[92]
				—	—	[102]
				—	93%	[93]
				—	710 μg/g	[103]
	C. frutescens	Green	MAE	Acetone (pure)	5.3 mg/g	[104]
				Ethanol (99.5%)	—	[105]
			UAE	Ethanol (95%)	87.4%	[106]
				Methanol (100%)	100%	[100]
				Acetone (100%)	3.92 mg/g	[107]
		Emergent	SFE	—	710 μg/g	[103]
				—	5.2%	[108]
	C. chinense	Green	UAE	Acetone (100%)	0.31 mg/g	[109]
				Methanol (100%)	2.88 mg/g	[110]
		Emergent	SFE	—	0.5%	[111]
	C. baccatum	Green	UAE	Methanol (100%)	50%	[112]
Antioxidants	*C. baccatum*	Green	UAE	Methanol (100%)	27%	[112]
OLEORESIN	*C. baccatum*	Green	UAE	Methanol (100%)	26%	[112]
	C. annuum	Green	EAE	Viscozyme L	6%	[101]
		Emergent	SFE	—	8.2%	[102]
				—	7.4%	[94]
				—	—	[113]
	C. frutescens	Emergent	SFE	—	0.3%	[108]
Other phytochemicals	*Capsicum* spp.	Green	UAE	Methanol (80%)	—	[114]

Table 6.
Bioactive compounds obtained from Capsicum *spp. extracted with different extraction methods.*

being this step the limiting stage. This method is used, for example, for the isolation of phenolic compounds of vegetable origin for their subsequent use in the food, pharmaceutical and cosmetic industries [115].

Water can be used as an extraction solvent, but it comes with the drawback is that it principally extracts the hydrophilic compounds present in vegetable materials. Several studies showed that water is not a very suitable solvent because its high polarity does not allow the extraction of capsaicinoids that are non-polar. However, it has the advantages or being safe, cheap and the simplest form to obtain essential oils. This technique can also be done with other solvents, being the ratio of solvent another parameter to take into account. Polarity is the reason why the most common solvents used are methanol, ethanol, water or a mixture of them [3].

Another parameter to optimize will be temperature. This makes it possible to differentiate two types of MA: cold maceration and heat maceration. Maceration with or without stirring, mild heating or heating under reflux are also possible variations to the method.

It is a quite old simple method with the inconvenience of long extraction times and large amounts of sample and solvents. Additionally, high temperatures can destroy thermolabile compounds such as phenolic compounds. In a study in which the effect of MA and ultrasound was related, it was detected that they have similar extraction yield of oleoresin; nevertheless, MA needs longer extraction times with the consequent loss of quality due to their higher times of exposure to high temperatures. It also was observed that n-hexane was a better solvent than ethanol [116].

4.1.2 Heat assisted extraction

This procedure is also a type of solid-liquid extraction in which the extraction is usually carried out in thermostatic and sealed water baths so that the solvent does not evaporate. The determining parameters are extraction time, temperature and the proportion of solvent that is used as well as the solid-liquid ratio. Due to the application of high temperatures (as far as 100°C), it is not the best extraction process for this type of matrix because certain compounds present in peppers (vitamins, phenolic compounds, etc.) are degraded by heat.

4.1.3 Cold pressure extraction

Cold pressure extraction is one of the oldest techniques of extraction for obtaining oils. It consists of mechanical pressing with the absence of heating. By using this method, little to no heat is generated, however it gives low yields. This technique was applied to Capia pepper seed, resulting in a lower extraction yield compared to traditional Soxhlet extraction with hexane. Moreover, the final oil was unpopular among consumers [117].

4.1.4 Organic solvent extraction

Organic solvent extraction (OSE) allows the extraction of many compounds (oils, fats and proteins). Normally, after the extraction process another step is done. It consists of concentrating the extract by removing the solvent under atmospheric or reduced pressure. OSE is the most extensively used technique to obtain oleoresins from peppers. These oleoresins are. Usually used as color additives [118]. In this method, the most determining limitation will be the solvent properties (polarity). When choosing the solvent, it must also be taken into account if the legislation allows its use. In the EU is regulated in Commission Regulation N° 231/2012.

In order to improve these conventional extraction techniques, other methods have been developed (ultrasound assisted extraction, pressurized hot water extraction, negative pressure cavitation-assisted extraction and pulsed electric) to partner with them and solve some of the inopportuneness of traditional techniques. In this way the extraction efficiency is substantially improved.

4.2 Green extraction techniques

This group includes several techniques with the aim of not only preventing pollution but also reducing sample preparation costs by, for example, lowering solvents consumption.

4.2.1 Microwave-assisted extraction

Microwave-assisted extraction (MAE) is based on the heating of solvents that are in contact with solid samples with the use of microwaves. This allows the partition of compounds of interest from the sample into the solvent. Microwave energy accelerates a great variety of chemical reactions as well as the extraction of organic compounds from different matrices [98]. During the process, electromagnetic energy is transformed into calorific energy by two mechanisms: ionic conduction and dipole rotation [119]. It is a method that could be an alternative for avoiding thermal degradation and oxidation, with no influence on cell integrity and shape. However, due to thermal stress and localized high pressures, cell rupture is more rapid than with another techniques, which is an inconvenience, for example, in the extraction of volatile oils [91].

Some of the advantages of this technique are simplicity, effectiveness, low processing time, low solvent consumption and energy, no generation of secondary waste and can be used for larger volumes [120]. Another advantage of this method is that it produces a uniform heating, so extraction is simultaneous regardless of the area where the compound is [121]. By using this method, lipids, pigments, carbohydrates, vitamins and proteins can be extracted [122]. Moreover, it is characterized by having a superior extraction rate of volatile compounds in *Capsicum* spp.

The selectivity and efficiency of MAE largely depends on the dielectric constant of the extraction solvent mixture, which defines its chemical polarity and thus what compounds will be extracted [91]. It can be expected that by using water as a single solvent, the quantity of capsaicinoids extracted decrease due to its negligible polarity [109]. Therefore, the parameters to take into account in this type of extraction are time, power, temperature and type of solvent and its ratios.

Several experiments can be seen in a summarized form in **Table 7**, which shows the variation between the values of the parameters among different experiments with solvents of different polarity. It is worth highlighting the values obtained for capsaicinoids using ethanol [105] as solvents since it is the one with the highest yield.

4.2.2 Ultrasound assisted extraction

In every extraction process there is a critical step which is the degradation of cell walls and membranes. Ultrasound assisted extraction (UAE) makes this possible by applying pressure waves that are transmitted across a medium as compression and expansion (rarefaction) cycles, finding an area with maximum pressure in the compression phase and one with minimum pressure in the rarefaction phase. This pressure difference makes the cavitation phenomenon possible, which breaks the

Target	Species	Extracting conditions				Yield	Ref.
		Temp.	Time	Power	Solvent ratios		
		°C	min	W			
Volatiles	*Capsicum annuum*	55	10	250	n-hexane (pure)	42 compounds	[59]
Pigments	*Capsicum annuum*	60	2	50	Acetone-water (50%)	—	[91]
Capsaicinoids	*Capsicum* spp.	21	15	300	Acetone (30%)	0.48 mg/g	[98]
	Capsicum chinense	50	5	800	Methanol (100%)	0.32 mg/g	[109]
	Capsicum frutescens	—	20	320	Ethanol (99.5%)	5.3 mg/g	[105]
	Capsicum frutescens	120	15	150	Acetone (pure)	0.673%	[104]
	Capsicum annuum	76	1	500	Methanol (60%)	230 ppm	[97]

—, *not described.*

Table 7.
Different experimental conditions carried out in peppers by microwave-assisted extraction.

structure to make the compounds accessible and therefore available to extract them [123].

This technique has been applied to extract different bioactive compounds from herbs or algae due to its ease to disrupt their cell walls despite its resistance which differentiates this method from the previous ones, since strong disruption of the cell wall is achieved and as a result the extraction of intracellular materials is increased with the increment of energy input [106, 120, 124].

The ultrasonic technique, as well as the other green techniques, has been proven to have several advantages such as reduction of solvents consumption, temperature and time, very important parameters in the extraction of thermolabile and unstable compounds as it has no effect on the chemical structure and biological properties. Furthermore, UAE has low equipment investment and easy implementation, so it can be basically industrially employed in local companies [106]. Moreover, there are studies that showed that this method also achieves a greater supercritical extraction of pungent compounds from ginger owing to physical effects on the surface of particles [106].

There are several parameters to take into account to optimize the method which include ultrasound power intensities, frequency, wavelength and time. There are several studies about it (**Table 8**). One of them studied the influence of several of these parameters on the extraction of capsaicinoids, observing that their release was very fast in the first 5 min of the process and then decreased. Temperature influence was also observed since an increase of 15°C (up to 45°C) improved the extraction using 95% ethanol (v/v) as a solvent. Higher temperatures did not lead to significant improvements [106]. The effect of the solvent was also studied, being the most common solvents used for extracting capsaicinoids methanol, ethanol, acetone, acetonitrile and water. It was proved that the yield of extraction is worse with the addition of water. Methanol and ethanol have similar recoveries but ethanol was better than acetone, the best concentration of ethanol being 95% [100, 106].

Target	Species	Conditions					Yield	Ref.
		Freq.	Intensity	Time	Temp.	Solvent		
		kHz	W/cm^3	min	°C	(%)		
Capsaicinoids	*Capsicum chinense*	20	—	10	40	Acetone (100)	0.31 mg/g	[109]
	Capsicum chinense	40	—	10	24	Methanol (100)	2.88 mg/g	[110]
	Capsicum annuum	31.5	—	20	76	Methanol (60)	200 ppm	[97]
	Capsicum annuum	—	—	20	50	n-hexane (100)	—	[99]
	Capsicum annuum	20	360	10	50	Methanol (100)	100%	[100]
	Capsicum frutescens	35	600	180	45	Ethanol (95)	87.4%	[106]
	Capsicum frutescens	20	360	10	50	Methanol (100)	100%	[100]
	Capsicum frutescens	—	—	40	25	Acetone (100)	3.92 mg/g	[107]
	Capsicum baccatum	20	150	20	40	Methanol (100)	50%	[112]
Antioxidants	*Capsicum baccatum*	20	150	20	40	Methanol (100)	27%	[112]
Oleoresin	*Capsicum baccatum*	20	450	20	60	Methanol (100)	26%	[112]
Phytochemicals	*Capsicum*	35	—	20	50	Methanol (80)	—	[114]

—, not described.

Table 8.
Different experimental conditions carried out in peppers by ultrasound assisted extraction.

4.2.3 Enzyme-assisted extraction

Enzyme-assisted extraction (EAE) is an extraction system that allows the avoidance of processing conditions like temperature or drastic pH changes and so, maintain the quality and yield of multiple biomolecules [125].

This type of extraction supports isolation for recovering bioingredients from different plant materials. An enzymatic pre-treatment before applying traditional methods will help to isolate high yields of bioingredients due to enzyme assisted extraction facilities. This is due to the fact that degradation of cell walls and membranes is the critical step of extraction which [101]. Among its advantages over traditional methods are high selectivity, overall efficacy, eco-friendly procedures, low-energy consumption, minimal usage of harsh chemicals, maximum yield, low to no wasteful protection or deprotection steps, easy recovery, and process recyclability [126]. However, it also presents some drawbacks such as the cost of enzymes, requirement of holding tanks that may require long term incubation, lack of knowledge about optimal or compatible enzyme formulations for cell disruption and inability to completely hydrolyse the bonds in plant cell wall [127].

The factors to take into account in this technique are fundamentally temperature, pH, and type of enzyme. A range of enzymes (lipases, carbohydrase, celluloses, proteases, pectinases) have been widely used as specific catalysts. Each enzyme has different substrates. For example, cellulase and hemi-cellulase have their greater hydrolysing activity on the cellulose found in plant cell walls, hence their name. This enzymatic processing increases the permeability of the cell wall, resulting in a better recovery of some compounds like volatile oil and resin, which are prone to degradation when extracted with more disruptive methods [101].

Several studies (**Table 9**) show that viscozyme L is an enzyme with a superior recovery rate of bioactive compounds fractions like total carotenoid content, total phenolic content, total flavonoids and total antioxidant activity with high total suspended solids (TSS). It also has at this moment the better extract yield [95, 96]. Among its applications is the extraction of pigments or capsaicinoids. In almost all cases the pH of the medium is 4.5 as it is the pH of the sample and it is in the range of optimal activity of the different enzymes [95].

4.3 Emerging technologies for extraction

Due to the disadvantages of traditional techniques, there is an interest in the development of new extraction techniques. Some of the most sought-after features include shortened extraction time, automation or reduced organic solvent consumption.

4.3.1 Hydrostatic high-pressure extraction

Hydrostatic high pressure (HHP) is considered an emerging technology that have been applied in the preservation of food since the end of eighties [128]. The first food products treated with this method began commercialization in Japan in 1990 [129]. This method is established on the application of high pressures (100–900 MPa) to the product of interest.

Among the advantages of this type of extraction there is the possibility to conduct it at room temperature, meaning no thermal degradation and derived bioactivity loss from extracted components. It also does not modify chemical structures of the different compounds of interest's independent form of molecular weight [130]. Moreover, in comparison with conventional techniques it is faster,

Target	Enzyme	Conditions			Yield	Ref.
		Temp	pH	Time		
		°C		h	%	
Carotenoids	Viscozyme L	60	4.5	1	87	[95]
	Pectinase	60	4.5	1	80	[95]
	Cellulase	60	4.5	1	low	[95]
	Viscozyme L	50	4.5	5	78	[96]
Capsaicinoids	Viscozyme L	50	4.5	5	88.8	[96]
	Viscozyme L	45	4.5	1	22	[101]
	Celluclast	45	4.5	1	20	[101]
Oleoresin	Viscozyme L	45	4.5	1	6	[101]

Table 9.
Different experimental conditions carried out in C. annuum *by enzyme-assisted extraction.*

gives higher extraction yields and fewer impurities [131] giving, unlike other preservation technologies as thermal treatment, uniform and nearly instantaneous effects throughout the foodstuff and thus independent of foodstuff geometry and equipment size which makes an easy scale-up from laboratory findings to full-scale production possible [132].

This method can be applied to multiple matrices for the extraction of natural compounds [133] like fruit and vegetables for different targets as for example carotenoids [134], antioxidants [131] and pigments [135].

The main parameters to be taken into account are pressure, time, temperature and type and quantity of solvent, studying each parameter for each variety in particular.

HHP can change physiological and biochemical properties of pepper based on a study carried out with *C. annuum* [136]. In this research, different pressures (50, 100, 200 and 300 MPa) where applied for 5 min at 25°C observing that it produces remarkable changes in seedlings, but no or very little physiological and biochemical variations, creating an antioxidant system that is positive for the plant itself in the process. Therefore, HHP (500 MPa) can be used as a preservation treatment similar to pasteurization which was the ttraditional thermal treatment for sweet pepper preservation [137].

4.3.2 Supercritical-fluid extraction

In supercritical-fluid extraction (SFE), the fluid must reach temperature and pressure above the critical point, so as the fluid behaves like liquid and gas simultaneously which makes extraction easier. This technology has been used in a wide diversity of fields (food, pharmaceutical, chemical and fuel industries) due to its advantages, there is an absence of toxic residue in the final product which allows not only the extraction valuable active compounds (fatty acids, pigments, polyphenols and vitamins) free of solvents, but also to remove undesirable compounds (pollutants, toxins and pesticides) [138]. Additional advantages are great extraction selectivity, short processing times, requirement of minimal solvents, low degradability of the extracted product and the fact that the remaining biomass can be treated with other techniques in order to continue extraction.

The most important conditions are temperature, pressure and co-solvent. The selection of each parameter will depend on the specific compound searched [138]. The most used solvent is CO_2 due to its thermodynamics and heat transfer properties. Moreover, it has a low critical point (31°C, 73 bar). Furthermore, the polarity of CO_2 can be modified by the use of co-solvents such as ethanol, and in this way also extract polar components.

Studies demonstrate that the extracts obtained with this technique are better than natural spice for flavoring purposes as SFE could reduce aflatoxin in the final products [139]. In addition, numerous bibliographic references show that carotenoid extraction is better at higher pressures [113].

Furthermore, when analyzing the extraction of β-carotene and capsaicin at the same time, capsaicin shows lower solubility, yet the solubility of β-carotene did not change in the presence of capsaicin, a factor to bear in mind when designing the separation process of coloring and hot components from paprika [140]. Several pepper species have been used to obtain natural compounds of interest using supercritical fluid extraction including capsaicinoids, oleoresins, pigments, tocopherols and even aflatoxins (**Table 10**) observing large variations between the pressures applied in each of the methods referred to in the bibliography. The greatest amount of studies is related to the specie *C. annuum* since it is the best known, widespread and cultivated specie of the genus *Capsicum*.

Target	Species	Pressure	Temp.	Flow rate	Time	Pepper	Yield	Ref.
		MPa	°C	cm s^{-1}	min	g	%	
Capsaicinoids	*C. frutescens*	20.5	40	0.064	10	50	5.2	[108]
	C. frutescens	7.84×10^{-3}	55	1	—	70	7.1×10^{-4}	[103]
	C. annuum	55	40	—	—	—	8.6	[92]
	C. annuum	12	40	—	390	—	—	[102]
	C. annuum	40	55	0.9–1.2[a]	—		93	[93]
	C. annuum	7.84×10^{-3}	55	1	—	250	7.1×10^{-4}	[103]
	C. chinense	15	60	2.15×10^{-3}	90	2.5	0.5	[111]
Oleoresins	*C. frutescens*	21.5	40	0.071	10	50	0.3	[108]
	C. annuum	30	40	—	360	—	8.2	[102]
	C. annuum	40	35	1–1.5	—		7.4	[94]
	C. annuum	43–54	40	1	—	25–30	—	[113]
Pigments	*Capsicum* spp.	47.5	80	sm	—	—	6	[90]
	C. annuum	36	45	—	—	—	17.4	[92]
	C. annuum	20	35	0.9–1.2	—	—	93	[93]
	C. annuum	40	35	1–1.5	—	—	7.2	[94]
Aflatoxins	*C. annuum*	30	50	—	2	7.8	16.2	[139]
Tocopherols	*C. annuum*	5	25	0.9–1.2[a]	—	—	84	[93]
	C. annuum	40	35	1–1.5	—	—	100	[94]

sm, semi-continuous; —, not described.
[a]*Propane.*

Table 10.
Different experimental conditions carried out in peppers by supercritical-fluid extraction.

4.3.3 Pulse electric field extraction

Pulsed electric field (PEF) consists of a non-thermal method that is extensively used in food processing applications due to, among other things, its ability to kill microorganisms in liquid foods. This method involves the application of short duration electric pulses, making several pores on the cell membrane in what is called electropermeabilization or electroporation. This makes it possible for the selective recovery of intracellular components with low energy consumption as the dielectric breakdown theory explains. According to this theory, the membrane of the cell has a low-dielectric constant that when exposed to a strong electric field provokes ion migration, forming free charges of the opposite sign which accumulate at both membrane sides, generating a potential difference across the membrane which depends on the size and shape of the cells and the concentration of cells in suspension. This difference in charges makes cell walls undergo a compression, reducing the membrane thickness that results in the formation of micropores and increasing permeability (electroporation) [119, 141]. It can be used directly or as a pre-treatment prior to solvent extraction [142]. The parameters to take into account with this method are number of pulses, length of the pulses, energy input and biomass concentration.

Among the advantages of PEF is the short extraction time (usually under 1 s), efficiency at low temperatures, decreased energy losses and a successful cell wall breakdown [120]. The disadvantages are that membrane changes can be reversible,

air bubbles make the process less effective and the efficiency of the method depends on electric field strength and electrode gap [142].

Further research is necessary since there is no data on the extraction of compounds with this technique. However, there are studies of the application of PEF for the production of dehydrated products or juices. As for drying, a study [143] done with red bell pepper at 320 J/kg, 2.0 kV/cm, 1 Hz and 30 pulses of 400 μs reported good results. Another study [144] with the same aim used different extraction conditions, which were 2.5 kV/cm, 100 Hz and 30 μs as the pulse time. As for juice production, *C. annuum* was studied with extracting conditions of 500 J/kg, 1.7 kV/cm, 1 Hz and 30 pulses of 300 μs demonstrating that juice from PEF treated paprika compared well in quality with enzymatic treatment [145].

5. Seed valorisation and industrial application

As it is being already done by some factories and companies in pepper growing countries, seeds, stalks or peels are extracted through whole fruit processing with or without semi-automated equipment. This is mainly done by the food industry in order to take away the non-edible parts of the vegetable to elaborate commodities as pepper powders (e.g., paprika), sauces, jams or pickled peppers. This way, stalks, seeds and placenta are usually removed and discarded.

But in many cases, placenta and seeds are subjected to extraction techniques in order to obtain essential oils to treat chronic ailments via topical administration in traditional remedies [146]. Even so, it is clear that pepper seeds are a multivalent source of many important compounds that could be used in different applications.

The elevated phenolic concentrations found in seeds make them an excellent target for extraction and use of these phenolic compounds, whether it is as antioxidant supplements, as food coating in order to increase shelf-life or as a potential source of functional animal feed. Moreover, the implementation of an extraction process in the food industry is dependent on the type of compounds of interest, as the yields of phytochemicals obtained may differ greatly. It should be noted that highly efficient and sustainable extraction methods continue to be a focus of research both in industry and academia [65].

Also, antimicrobial potential of phytochemicals present in pepper should be considered. Even though this would involve highly specialized equipment and maintain strict aseptic conditions, there is promise in their use as food preservers from common food-borne pathogenic microorganisms besides their antioxidative capability. Furthermore, their use as alternative antibiotics has hardly been researched and the safety of their administration or clinical use has not yet been assessed.

Regarding their nutrition attributes, the high linoleic acid and palmitic acid present in the seeds could lead to use them as a primary source of cooking oil, or as a main component in foods such as margarine, or preserver in certain pickled products [48]. Also, as they are a rich natural source of vitamins E and C, extracts of these vitamins could also be incorporated as constituents of many juices and other foods. Pepper-processing industry could find very rewarding to investigate on the yet unknown beneficial properties of its by-products and obtain additional profit by integrating existing extraction and purification technologies into their process chain.

6. Conclusions

It is clear that the wide spectrum of historical applications of peppers is supported by the latest findings on the properties of peppers. The diversity among

Capsicum species properties have been studied over the years, although many of the possible bioactivities have only been characterized in the whole fruit and there are few *in vivo* experiments reported testing phytochemicals of this genus or assessing its safety. Moreover, research on produce by-products has acquired weight within the scientific community and industry as of lately. The exploitation of food processing by-products means not only an affordable raw material for the extraction of valuable phytochemicals, but also a reduction of ecological and economic impact of agricultural and industrial activities. Further studies are necessary to explore in depth more efficient bio-active compounds from the underutilized and non-edible biomass of *Capsicum* spp. Furthermore, the great genotypic diversity of the many pepper varieties grown in different regions, have a high variety of bioactive compounds, some still to be discovered. Currently available knowledge about the medicinal phytochemicals found in the genus *Capsicum* should be considered to develop novel drugs to treat many diseases and ailments.

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Author details

Javier Echave[1], Antía G. Pereira[1,2], María Carpena[1], Miguel Ángel Prieto[1*] and Jesús Simal-Gandara[1*]

1 Nutrition and Bromatology Group, Analytical and Food Chemistry Department, Faculty of Food Science and Technology, University of Vigo, Ourense, Spain

2 Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Bragança, Portugal

*Address all correspondence to: mprieto@uvigo.es and jsimal@uvigo.es

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