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The Orange Peel: An Outstanding Source of Chemical Resources

Gianfranco Fontana

Abstract

Citrus sinensis (L.) Osbeck is a very common cultivar belonging to the *Rutaceae* family. It is largely diffused in several areas of the world characterized by mild to warm climate conditions. Its abundant worldwide production (up to 10^7 Tons. per year) and consumption both as the edible part of the fruit and as several types of derivative products imply the production of a huge amount of waste, such as the fruit pomace. Several ways of recycling this material have been developed in recent years: employment as fertilizer, fodder ingredient, and even cloth material. However, the chemical added value of *Citrus sinensis* peel has been underestimated despite the diversified and significant content of useful chemicals, such as polyphenols, polymethoxylated phenols, glycosylated flavonoids, volatile and non-volatile terpenoids, pectins, enzymes, etc. This work aims to highlight the outstanding chemical potential of *Citrus sinensis* peel.

Keywords: biological activity, *Citrus sinensis*, essential oil, flavonoids, orange peels, polymethoxyphenols

1. Introduction

Citrus sinensis (CS) (L.) Osbeck is a perennial species growing in warm climate areas of the world and largely employed as food in form of fresh fruit, with a global production of ca. 6.7×10^7 tons. per year (TPY) in 2016 [1], or as a processed derivative (ca. 1.85×10^7 TPY) such as juice, marmalade, flavor, fragrance and coloring additive, pectin.

CS is an evergreen tree, 3 to 9 mts. high with sparingly barbed branches, alternate leaves with toothed blades differently shaped, oval or elliptical, connected to the stem by winged-petioles. Axillary flowers are present singly or in whorls of 6 and possess 5 white petals and up to about 25 yellow colored stamens. The pericarp of CS has a spherical or oval shape of 6–10 cm diameter with the color changing from green to yellow-orange during the ripening; the endocarp containing juice sac glands is enclosed within a wrinkled epicarp or exocarp or flavedo containing a great number of essential oil glands protected by a waxy epidermis. Below the flavedo is the albedo, also called mesocarp, a white filamentary tissue composed of tubular-like cells.

The principal industrial application of CS is the production of frozen concentrated juice. The procedure of juice extraction eventually accompanied by the extraction of the essential oil, implies the generation of a major “by-product” constituted by a pomace, mainly containing peels, accounting for up to around 60% w/w of the original fruit mass processed [2]. This huge amount of biomass does pose

serious environmental concerns because of its high level of total organic carbon (TOC) and biological oxygen demand (BOD) that make disposal procedures rather complex and demanding from both the legal and industrial points of view. This is because there is an increasing trend to modify the way of approaching this problem by reconsidering the post-production orange pomace more like a by-product rather than a waste. In the last years, many producers have subjected this material to processings involving partial acidic fermentation, drying, and packaging to biologically and chemically stabilize the biomass before its application as animal feed in zootechnics, soil conditioners in agriculture, or the manufacturing of compost and biogas [2].

Beyond the standard workup of the *Citrus sinensis* peel (CSP) waste, new perspectives have been being opened in the context of the high chemical added value of the CSP [3–5] also by the complete knowledge of the rich metabolomics profile of this species. The use of CS peel has been proposed for a variety of purposes that include the production of antioxidant-enriched dietary supplements in veterinary [6], the preparation of human dietary supplements, and nutraceuticals such as citric acid [7] and flavonoids [8, 9]. The extract of CS peel is the source of a huge variety of phytochemicals and has been investigated on several applications including its chemotherapeutic and chemopreventive potential for several relevant human pathologies, such as cancer [10, 11] and obesity [12]. The extraction procedures vary in function of the main components that have to be obtained: from the simple cold pressing of pomace and the extraction with water to obtain highly hydroxylated compounds to the employment of mixtures organic protic solvent/water and finally low polar organic solvents such as Chloroform and Ethyl acetate to obtain polymethoxylated phenols (PMF, see below). New extraction technologies such as ultrasounds and microwaves may help to obtain better extraction yields.

In the following sections, the chemical structures and the biological effects of these compounds will be discussed.

2. The chemistry of *Citrus sinensis* peel

2.1 Essential oils

The essential oil (EO) is mainly obtained from the CS peel as a major by-product of the juice production process by a cold-pressing method that can provide the intact blend of compounds without losing the lighter, more volatile, components of the complex mixture that can be lost in the standard EO extraction procedure that is the hydrodistillation. The last one is mainly used in small scale applications, for example in research laboratories.

The chemical composition of CSP EO [13–15] is reported in **Table 1**. As it can be seen, the major component is D-Limonene, accompanied by several minor components belonging to the classes of monoterpene alkenes, oxygenated monoterpenes including alcohol aldehydes and esters, sesquiterpenes as well as linear alkanes and aldehydes. This rather complex blend accounts for the numerous deal of biological activities reported for the CSP EO [14–16], which include anthelmintic, anti-aflatoxigenic [17], antibacterial [18–20], anticarcinogenic, antifungal [21], antioxidant [17], anti-tumor [22], anxiolytic [23], food preservative [24], hepatocarcinogenesis suppressant, insecticidal and larvicidal [25], pain relief and relaxant [26]. It can be argued that the main effects are due to the presence of the major component Limonene that showed several bioactivities when tested as pure compound [27]. However, it is possible that synergistic effects due to the combination of Limonene with other minor components may be speculated and should have to be demonstrated.

Comp.	Comp. name	%	Compound.	Comp. name	%
1	Aromadendrene	0.01	21	β -Linalool	0.4–5.6
2	δ -Amorphene	0.05	22	β -Myrcene	1.3–3.3
3	D-Cadinene	0.01–0.03	23	Neral	0.1–1.3
4	δ -3-Carene	0.18	24	Neryl acetate	0.02
5	β -Citral	0.12–0.15	25	Nonanal	0–0.1
6	L-(+)-Citronellal	0.01–0.1	26	Nootkatone	0.01
7	Citronellyl acetate	0.01	27	<i>cis</i> - β -Ocimene	0.03–0.26
8	α -Copaene	0.04	28	Octanal	0.02–0.8
9	α -Cubebene	0.02–0.26	29	Perillaldehyde	0.03
10	β -Cubebene	0.03	30	α -Phellandrene	0.02–0.07
11	Decanal	0.04–0.4	31	α -Pinene	0.49–0.59
12	n-Dodecanal	0.06	32	(+)-Sabinene	0.2–1.0
13	β -Elemene	0.01–0.02	33	γ -Terpinene	0–1.21
14	Geranial	0–1.8	34	γ -Terpineol	0.04–0.08
15	Germacrene-D	0.02–0.08	35	α -Terpineol	0.07–0.42
16	β -Gurjurene	0.01	36	Terpinolene	0–0.08
17	Hexadecanol	0.04	37	α -Thujene	0.04
18	D-Limonene	Ca. 95			
19	L-Limonene	0.02			
20	<i>trans</i> -Limonene oxide	0.01			

Table 1.
Composition of C. sinensis essential oil obtained from peels.

2.2 Polyphenols

2.2.1 Flavanoids

Polyphenols extracted from the CS peel belongs to the general structural categories of flavanones (**Figure 1a**), flavones (**Figure 1b**), flavonols (**Figure 1b**), with and without sugar moieties attached to one or more of the hydroxyl groups [28]. It is worthy of particular mention the rarely occurring class of C-glycolflavones (**Figure 1b**, compounds **63–65**, **85**, **86**).

These compounds are produced *in vivo* from the biogenetic mixed pathway of the Acetate and Shikimate that implies the enantiospecific formation of the basic aromatic bicyclic framework of the flavanone, from which a huge number of flavonoids originate employing selective enzymatic hydroxylations, methylations, and glycosylation steps. As can be seen from the structures shown in **Figure 1**, most of the chemical entities found in the peel extract contain several methoxy fragments that decorate the carbon skeleton. This characteristic makes those molecules to get a rather apolar character that explains their presence in the hydrophobic environment of the waxy peel. On the contrary, compounds containing a major number of hydroxyl groups are less present in the peel and are instead more significantly concentrated in the juice of the pericarp. However, some glycosylated compounds are present in the peel. In these molecules, the aglicone bears a monosaccharide unit (mainly glucose) or a disaccharide, in most of the cases being

Rutinosyl (**91**) – Rhamnosyl ($\alpha 1 \rightarrow 6$) glucose – or Neohesperidose (**92**)- Rhamnosyl ($\alpha 1 \rightarrow 2$) glucose (**Figure 2**).

The composition of the peel extracts described in the literature may slightly vary depending on the cultivar and the region of harvesting but some general points are

Cm p.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Name
38	H	H	H	H	Me	OH	Hesperetin
39	H	H	Rut	H	Glu	H	Narirutin-4'- glucoside
40	H	H	Rut	H	Me	OH	Hesperidin
41	H	H	Neohesp	H	Me	OH	Neohesperidin
42	H	H	Rut	H	H	H	Narirutin
43	H	H	Rut	H	Me	H	Didymin
44	H	H	Glu-Glu	H	H	H	Naringenin-7-O- bglucoside
45	M e	OMe	Me	H	Me	H	5,6,7,4'- tetramethoxyflavano ne
46	H	OMe	Me	OMe	Me	OMe	5-hydroxy-6,7,8,3',4'- pentamethoxyflavano ne
47	H	H	Neohesp	H	H	H	Naringin

Cmp.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	Name
48	H	H	H	H	H	H	H	Apigenin
49	H	H	H	H	Me	H	H	Acacetin
50	Me	OMe	Me	H	Me	H	H	Tetra-O- methylscutellarein
51	Me	OMe	Me	H	Me	OMe	H	Sinensetin
52	Me	OMe	Me	OMe	Me	H	H	Tangeretin
53	Me	OMe	Me	OMe	Me	OMe	H	Nobiletin
54	Me	OMe	Me	H	Me	OMe	OMe	Hexa-O- methylquercetagenin
55	Me	OMe	Me	OMe	Me	OMe	OMe	3',4',3,5,6,7,8- Heptamethoxyflavone
56	H	H	H	H	Me	H	OH	Kaempferide
57	H	H	H	H	H	H	OH	Kaempferol
58	H	H	H	H	H	OH	H	Luteolin
59	H	H	H	H	H	OH	OH	Quercetin
60	Me	OMe	Me	OMe	Me	OMe	OH	Natsudaidin
61	Me	OMe	Me	OMe	Me	H	OH	3-hydroxy-5,6,7,8,4'- pentamethoxyflavone
62	Me	OMe	Me	H	Me	H	OH	3-hydroxy-5,6,7,4'- tetramethoxyflavone
63	H	H	H	C- Glu	H	H	H	Vitexin
64	H	C- Glu	H	C- Glu	H	H	H	6,8-di-C- Glucosylapigenin
65	H	C- Glu	H	C- Glu	Me	OH	H	6,8-di-C- Glucosyldiosmetin

66	H	H	Me	H	H	OMe	O-Glu	
67	H	H	Me	H	H	H	H	5,4'-dihydroxy-7-methoxyflavone
68	H	H	H	H	H	OH	O-Glu	isoquercetin
69	Me	H	H	H	H	H	O-Rut	5-Methyl-3-ruthinoxylKaempferol
70	Me	H	Me	H	Me	OMe	H	5,7,3',4'-tetramethoxyflavone
71	H	H	H	H	H	OH	O-Rut	Rutin
72	H	H	H	OH	H	H	H	Iscoscutellarein
73	H	H	Me	H	Me	OMe	OMe	5-hydroxy-3,7,3',4'-tetramethoxyflavone
74	H	OMe	Me	H	Me	OMe	OMe	5-hydroxy-3,6,7,3',4'-pentamethoxyflavone
75	H	H	Me	OMe	Me	OMe	OMe	5-hydroxy-3,7,8,3',4'-pentamethoxyflavone
76	H	OMe	Me	H	Me	H	H	5-hydroxy-6,7,4'-trimethoxyflavone
77	H	OMe	Me	H	H	H	H	5,4'-dihydroxy-6,7-dimethoxyflavone
78	H	OMe	Me	OMe	Me	H	H	5-hydroxy-6,7,8,4'-tetramethoxyflavone
79	H	OMe	Me	H	Me	OMe	H	5-hydroxy-6,7,3',4'-tetramethoxyflavone
80	H	OMe	Me	OMe	Me	OMe	OMe	5-hydroxy-3,6,7,8,3',4'-hexamethoxyflavone
81	H	OMe	Me	OMe	Me	OMe	H	5-hydroxy-6,7,8,3',4'-pentamethoxyflavone
82	H	H	Rut	H	H	OH	H	Luteoline-7-O-rutinoside
83	H	H	Rut	H	H	OMe	H	Chrysoeriol-7-O-rutinoside
84	H	H	Rut	H	Me	OH	H	Diosmin
85	H	C-Glu	Rut	H	Me	OH	H	6-C-b-glucosyl diosmin
86	H	C-Glc	Rut	C-Glc	Me	OH	H	6,8-di-C-b-glucosyl diosmin
87	H	H	Rut	H	H	H	H	Isorhoifolin

Glu: Glucose, Neohesp: Neohesperidose, Rut: Rutinose.

Figure 1.
Chemical structures of flavonoids from *C. sinensis* peels.

common, that is the presence of the high amount of bioactive polymethoxy-flavonoids [29, 30](PMF) some of which are rather ubiquitous, e.g. Nobiletin 53, Sinensetin 51, 3',4',3,5,6,7,8-Heptamethoxyflavone 55; some other compounds

Figure 2.

Chemical structures of the disaccharides most commonly bound to flavonoids of *C. sinensis* peel.

containing one to six methoxy groups in place of the hydroxyl groups are present at variable amounts. The presence of one or more residual hydroxy groups in the molecule may result in a higher bioavailability and in other general differences in their mechanism of biological and therapeutic actions [30, 31].

The biological role of these secondary metabolites in the plant is still matter of debate. It has been proposed their involvement in the mechanism of defense of the fruits exposed to the attack of phytopathogens, such as *Phytophthora citrophthora* [32].

Further, the composition of the PMF blend can be employed for the chemiotaxonomic characterization of the *Citrus* genus [33].

However, it needs to be stressed that in many cases the reported compounds were recognized by mass spectrometry and electronic spectroscopy. It is not always a matter of simplicity to discern the exact structure of a given PMF and to discriminate between different regioisomers, normally quite similar in terms of mass and electronic spectra, if an isolation procedure is not conducted and followed by a complete bi-dimensional NMR characterization. Significant differences in the extract composition do arise also in consequence of the extraction method; non-polar solvents such as Methanol, Chloroform Ethyl acetate let to obtain PMFs-rich extracts while, on the other hand, hydroalcoholic and aqueous extracts do contain a low concentration of PMFs and a higher concentration of un-methylated polyphenols as well as glycosylated compounds.

The biological activities disclosed for the flavonoids extracted from CSP are variegated. They include antioxidant [9, 34–39], anti-inflammatory [40, 41], antimicrobial [39, 42–44], antimalarial [45], antitrypanosomal [46], cardio-protective [47], anti-osteoporosis [48], anti-ulcer [49], vascular protective [50], anti-diabetes [51, 52], hepatoprotective [53, 54], neurotrophic [55], anti-adipogenesis and anti-obesity [56–58], anti-hypertensive [59], cataract prevention [60], sun protection [61], metabolic syndrome control [62]. Further, it has been demonstrated [63] that while both flavonoid set **40**, **42**, **43** and the PMFs **51–53** were able to inhibit the anion transportin polypeptide OATP2B1 in HEK293 cells, only the PMF group displayed this inhibitory activity also for the OATP1B1 and OATP1B3 carriers.

The most abundant PMF occurring in CSP, Nobiletin **53**, was proven to possess several bioactivities, such as antioxidant, anti-inflammatory, cancer preventive [64] and also a significant protective effect *in vivo* against the endotoxic shock [65] and ethanol-induced acute gastric lesions [66] in mice. Further, compound **53** demonstrated the capacity to induce autophagy in human keratinocyte HaCaT cells [67], vasodilator effect in the rat aorta [68] and to protect the intestinal barrier from the damages induced by dextran sulfate sodium [69].

PMFs can be considered as especially promising lead compounds for cancer therapy as significant cytotoxic activity has been demonstrated toward a number of cancer cells [70, 71] with several mechanisms of action [72, 73]; the cell types investigated include MCF-7 [73–76], Hs578T triple-negative breast cancer [73, 77]; colon cancer cells CaCo-2 [19], LoVo [78], HTC-116 [79, 80] and HT-29 [79, 81]; lung cancer cells A549 [80, 82], H460 [82, 83], H1299 [82, 83]; gastric cancer cell lines AGS, BGC-823, and SGC-7901 [84]; leukemia cells HL-60 [85]. However, data regarding a possible antitumor activity *in vivo* are still rather uncommon. An interesting example is the case of the significant reduction of the intestinal tumor mass in ApcMin/+ mice treated with a CSP extract containing various PMF [86]. Further, CSP extract and pure Naringin **47** were tested for their efficacy against a YM1 esophageal cancer in an animal model [87].

Given the development of pharmacological applications of CSP extract components, further investigations are needed to better understand the bioavailability, safety, and efficacy of these compounds in humans. Most of the data reported concern *in vitro* experimentations or animal model tests. For example, the toxicity of Hesperidin **40** was evaluated [88] in Sprague Dawley rats showing a 50% lethal dose (LD50) of about 5 g/Kg body weight (BW) and a lowest-observed-adverse-effect level (LOAEL) of ca. 1 g/Kg BW.

In general, it should be emphasized as the body of evidence concerning the actual efficacy of sweet orange-derived compounds in human health is still far to be exhaustive. For example, while this work is under typewriting, a severe acute respiratory syndrome pandemic due to a COVID-19 virus is in act and a big deal of research has been being directed toward antiviral remedies and therapies. Research on nutraceuticals is not an exception and in particular some authors have shown by computational and molecular docking methods how Hesperidin **40**, the most abundant polyphenol obtained from *C. sinensis*, would be able to bind the spike protein of this virus thus inhibiting its activity [89]. Despite their undoubted interest, these results need to be further investigated with different experimental approaches.

The pharmacological potential of pure Hesperidin **40** was also investigated for several relevant human morbidity, such as cancer, hypertension, and ulcer [90].

2.2.2 Hydroxy-acids

Several hydroxylated carboxylic acids belonging to several structural sub-classes are present foremostly in the extract obtained with mixed hydro-organic solvents, such as MeOH/water and EtOH / water [37, 38, 51, 78]; these include the aliphatic Ascorbic, Citric, Kojic, Lactic, and L-Malic acids; the aromatic 4-Hydroxybenzoic, Protocatechulic, and Gallic acids. Further, the cinnamyl compounds (**Figure 3**) Cinnamic (**93**), p-Cumaric (**94**), Caffeic (**95**), Ferulic (**96**), Sinapinic (**97**) acids, and Artepillin (**98**) were identified in some CSP extracts that showed relevant biological activities, such as antioxidant [34, 37, 38] and antidiabetes [51].

These organic acids are mainly found in free form but in some cases, they are esterified with a variety of alcoholic compounds, such as Ethanol in Ethyl gallate **99** [51], 2-Phenylethanol in Phenylethyl ester of Caffeic acid **100** [51] and (–)-Quinic acid in Chlorogenic acid **101** [51]. An interesting ester derivative (**102**) in which the anomeric hydroxyl of Glucose is esterified with a O-Caffeoylsinapoyl acid unit was found in the methanolic extract of a Greek cultivar of *C. sinensis* [34].

It was shown [38] that the antioxidant properties of a CSP extract better correlated with the total phenols content (TPC) of the sample rather than with its total flavonoid content (TFC), as it can be expected from the known relevant antioxidant character of hydroxycinnamic derivatives.

Figure 3.
Chemical structures of cinnamic acids extracted from *C. sinensis* peels.

2.2.3 Coumarins

Coumarins are aromatic compounds biogenetically related to the o-hydroxysubstituted cinnamic acids from which originate by the intramolecular condensation between the carboxylic and the o-hydroxy groups. These compounds are most commonly encountered in other species of *Citrus* taxa [91], such as *C. aurantium* (bitter orange), *C. limon*, (lemon), *C. limetta* (lime), *C. paradisi* (grapefruit) and only a few molecules of this class were Isolated from extracts of CSP endowed with activity against osteoporosis [48] and antioxidant [92]; these compounds are shown in **Figure 4**. As coumarins are relatively less common in *C. sinensis* cultivars compared to other species of the *Citrus* taxa, their rarity can be considered as a chemotaxonomic marker for *C. sinensis*.

2.2.4 Catechins

The NADPH dependent bioreduction of flavanols is the biogenetic origin of this class of compounds, present as minor constituents in CSP extract possessing significant antioxidant activity [38]; they are the two enantiomeric forms Catechin **113** and Epicatechin **114**, together with Epigallocatechin **115** (**Figure 5**).

Figure 4.
Chemical structure of coumarins extracted from *C. sinensis* peels.

2.3 Pectins

Pectins [93] are chemically definable as complex mixtures of polyglyconic acids in which a linear polymeric backbone is structured by a series of α (1 $\rightarrow$ 4) linkages (**Figure 6**). The main sugar monomer is always Galacturonic acid with the presence

Figure 5.
Chemical structure of catechins from *C. sinensis* peels.

Figure 6.

Minimal representation of a Homopolygalacturonic acid domain of the linear primary pectin structure with a 1/3 Mol. /Mol. Esterification degree.

of possible heterogeneous domains of other sugars such as Xylogalacturonan and Rhamnogalacturonan-I. A variable amount of the free carboxy functions may be esterified with methyl groups, while the hydroxy groups at C-2 and C-3 positions of the sugar monomers may be acetylated. Even though the primary structure of the main chain is linear, a possible degree of ramification, depending on the pectin source, may also be found. The differences in the pectins composition and structures, depending on their natural source, do confer them different physio-chemical properties, such as water solubility, sol-gel concentrations, etc. On the ground of the degree of methylation of the acid moieties, pectins are classified as “low methoxyl” (LMP, $-\text{COOMe}/-\text{COOH} < 50\%$ mol.) or as “high methoxyl” ($> 50\%$ mol). A simplified representation of pectin structure is given in **Figure 6**.

Pectins find many applications in the food and drug industry as a thickening and gelling agents, excipients, and colloidal stabilizers [93].

As it has been already mentioned, the extraction method does affect the structure and the properties of the final product; the traditional acidic water extraction implies a certain degree of hydrolytic deterioration, so that new extraction technologies have been being investigated to improve the quality of the final pectins, that is microwave-assisted extraction (MAE) [94] and ultrasounds assisted extraction (USAE) [35, 95].

2.4 Enzymes

As it can be easily argued, the CSP cellular system, whose genomic profile has been fully characterized [96], is the site of a complex network of enzymatic activity. Some of the enzymes of CSP have been characterized and employed in many applications.

The acetylsterase (international enzymatic classification: EC 3.1.1.6) from CSP is known since 1947 [97] and was isolated and characterized [98]. The acetylsterase activity of the partially purified enzyme was used for the removal of the acetyl group at the 3 positions of β -lactamic antibiotics **116** [98] (**Figure 7a**). Further, the whole CSP, as well as pomace from the industrial waste of the orange juice production, was successfully employed to catalyze several relevant biotransformations [99] such as the conversion of Geranyl acetate **118** to Geraniol **119** (**Figure 7b**) and the di-acetoxynaphtalene derivative **120** to the vitamin k1 precursor **121** (**Figure 7c**).

Figure 7.
Chemical reactions biocatalysed by enzymes from *C. sinensis* peels.

Recently, partial purification and functional characterization of a Uronic acid oxidase from CSP was accomplished [100]; this enzyme promotes the oxidation by O_2 of Galacturonic acid **122** to Galactaric acid **123** (Figure 7d).

2.5 Miscellaneous

2.5.1 Highly lipophilic compounds

The waxy environment of flavedo in CSP does contain several long-chain saturated and unsaturated compounds: alkanes, fatty acids, waxes, higher terpenoids.

Tetracosane, Tetratriacontanoic acid, and Ethyl pentacosanoate were identified in CSP of a Pineapple variety [101]. Further, some carotenoids were identified in the CSP extract obtained with a solvent mixture composed of Ethanol, Ethyl acetate, Petroleum ether 1: 1:1 [102]. This complex blend of carotenoids includes α - and β -Carotene, Phytoene, Phytofluene, (all-E)- and (9Z)-Violoxanthin, (all-E)-Neoxanthin, (13Z)-, (13Z')- and (all-E)-Lutein, (9Z)-Zeaxanthin, (all-E)-Zeaxanthin; the mono and di-esters of violaxanthin, antheroxanthins, Xanthophyll, β -Citaurin with various fatty acids, including Lauraic, Myristic, Oleic, Palmitic, Stearic. The composition of the blend has been correlated with the maturity stage of the fruit.

Figure 8.

Primary structure of cyclic peptide isolated from the *C. sinensis* peels.

2.5.2 Peptides

Three cyclic peptides have been isolated from the hot water extract of CSP and were structurally characterized by FAB-MS and 2D-NMR techniques [103]. Their amino-acidic sequences, including a mostly lipophilic heptapeptide **124**, a di-hydroxylated heptapeptide **125**, and a Glutamate-rich octapeptide **126**, are reported in **Figure 8**.

3. Conclusions

The chemical richness of the primary and secondary metabolome of *C. sinensis* species is undoubtedly impressive. Thousands of different compounds belonging to dozens of structural classes have been isolated and described. The most deeply investigated are sure, on one hand, the mixtures of volatile compounds composing the blend of the essential oil and, on the other hand, polyphenols, especially flavonoids.

The chemical composition of the extract from the exocarp of *C. sinensis* does differ from the composition of juice, or leaf extracts for some aspects [104]: the presence of a higher amount of more lipophilic compounds such as polymethoxy-flavonoids, r carotenoids, higher alkanes; a lesser extent of lighter terpenoids, a lower content of glycosylated compounds, the absence of cyanidins and sterols.

It is also a matter of fact that several interesting bioactivities were disclosed in the last years for the *C. sinensis* extracts that have been variously associated with the well-recognized beneficial effects that regular sweet oranges consumption may have on human health. However, a great deal of research work is still needed to clarify the molecular basis and the mechanism of these chemopreventive effects and to relate them with precise chemical entities that can be recognized as valuable nutraceuticals, as it is already the case for the well-established antioxidants Ascorbic acid, Hesperidin, Hesperetin, Quercetin, etc.

Conflict of interest

The author declares no conflict of interest.

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