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Review

Carnosic Acid and Carnosol: Analytical Methods for Their Determination in Plants, Foods and Biological Samples

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Abstract: Among the various phytochemicals, which are present in Lamiaceae plants, carnosic acid and carnosol stand out. Carnosic acid is a phenolic diterpene carrying two phenolic hydroxyl groups and a carboxyl group, while carnosol carries a lactone moiety in addition to phenolic hydroxyls. Both these phenolic diterpenes exhibit interesting biological properties, such as antioxidant, anticancer, anti-inflammatory and neuroprotective activities. In this review, we summarize the existing analytical methods for the determination of carnosic acid and carnosol, primarily in plants, but also in foods and biological samples. Due to the biological importance of carnosic acid and carnosol, a variety of analytical methods, including high-performance liquid chromatography–ultra violet (HPLC–UV), liquid chromatography–mass spectrometry (LC–MS) and capillary electrophoresis (CE), were developed for their determination. In addition, we discuss the extraction methods applied for their isolation from plants and in brief the bioactivities of these phytochemicals.

Keywords: carnosic acid; carnosol; HPLC–UV; LC–MS; phenolic diterpene

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1. Introduction

The family of Lamiaceae or Labiatae plants, which includes rosemary (*Salvia rosmarinus*, synonym *Rosmarinus officinalis*), sage (*Salvia officinalis*), thyme (*Thymus vulgaris*), lemon balm (*Melissa officinalis*) or wild marjoram (*Origanummajorana*), is an enriched source of antioxidant compounds, such as phenolic acids, flavonoids and terpenes [1,2]. Most of these plants are native to the temperate Mediterranean region and are exported worldwide either as extracts or in their dried form [1–3]. In rosemary and sage, the major bioactive components are rosmarinic acid, carnosic acid and carnosol (Figure 1) [4]. Carnosic acid is a phenolic diterpene carrying two phenolic hydroxyl groups and a carboxyl group. When oxidized, carnosic acid can be directly converted to carnosol with hydroxyl groups at positions C-11 and C-12 and a lactone moiety. Carnosol can in turn be converted into rosmanol or epirosmanol by hydroxylation at C-7 on its lactone ring (Figure 1) [5]. Carnosic acid can also form methyl carnostate by be methylation of the carboxyl group.

Carnosic acid, carnosol and their derivatives are normally found in photosynthetic green tissues, e.g., sepals, leaves and petals of plants, specifically in the chloroplasts [6]. The contents of these bioactive components in rosemary plants grown in fields display seasonal fluctuations, and in particular, carnosic acid contents tend to decline in response to conditions of environmental stress, i.e., high temperatures and/or low precipitation rates during summer [7].

Simultaneously, an increase in oxidized metabolites was observed, suggesting that cellular oxidative stress is evidently accompanied by the decrease in carnosic acid levels [8,9]. Environmental stress strongly influences the synthesis of bioactive compounds due to the generation of excess ROS free radicals, triggering the biosynthesis of secondary ROS scavenging systems. As a consequence, diterpene derivatives, such as carnosic acid, and their oxidized derivatives can be acknowledged as biomarkers of the environmental stress in plants such as sage and rosemary [10,11].

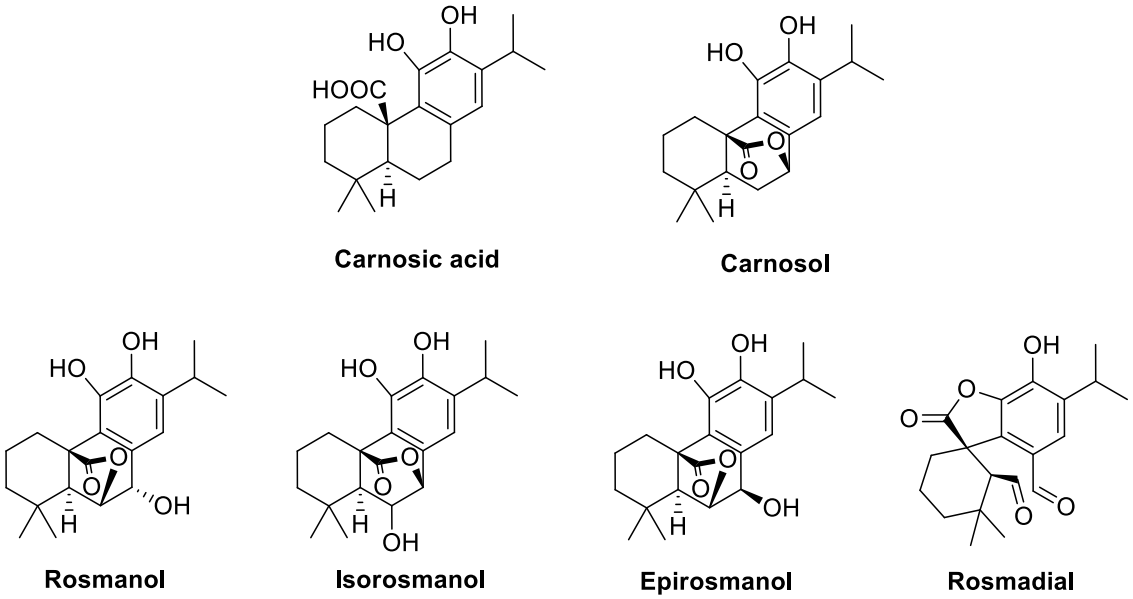

Figure 1. Structures of carnosic acid, carnosol and their derivatives.

Table 1 summarizes the presence of carnosic acid, carnosol and their derivatives in various Lamiaceae plants. Specifically, all derivatives were identified in rosemary and sage extracts [12,13]. Carnosic acid, carnosol and methyl carnosate were also identified in oregano extracts [14], while carnosol and methyl carnosate were detected in thyme extracts, where carnosic acid was absent [14]. Finally, in marjoram extracts, both carnosic acid and carnosol were detected [15], while lemon balm was only found to contain carnosic acid [16].

Table 1. Carnosic acid, carnosol and their derivatives in Lamiaceae plants.

Lamiaceae Plants	Carnosic Acid	Carnosol	Rosmanol	Epi-, iso- Rosmanol	Rosmadial	Methyl Carnosate
Rosemary	X	X	X	X	X	X
Sage	X	X	X	X	X	X
Oregano	X	X				X
Thyme		X				X
Lemon balm	X					
Marjoram	X	X				

Rosemary extract is employed in food industry as a result of its established high antioxidant activity. In the European Union, rosemary extract is assigned as an antioxidant food additive (E 392), with an acceptable daily intake of 0–0.3 mg/kg body weight, expressed as the sum of carnosic acid and carnosol [17]. Rosemary extracts were added to lipids or foods containing lipids, such as plant seed oils, fish oils, fat-based spreads and meats, to prolong their storage life [18].

Because of the importance of the plant bioactive components carnosic acid and carnosol, a variety of appropriate extraction and analytical methods, resulting in high recovery, sensitivity and reproducibility, were developed. The aim of this review article is to summarize the existing analytical methods, which include high-performance liquid chromatography–ultra violet (HPLC–UV), liquid chromatography–mass spectrometry (LC–MS) as well as capillary electrophoresis (CE) techniques. Furthermore, the extraction procedures and the sample preparation methods and in brief the bioactivities of carnosic acid and carnosol are discussed.

2. Extraction Methods

Extraction is a crucial and essential process for the isolation of bioactive components from plants in concentrated forms of higher purity. The development of new effective

extractive procedures with high recovery yields and better selectivity is always an important and popular research topic [19]. Regarding bioactive compounds with antioxidative properties, such as carnosic acid and carnosol, some parameters that must be taken into consideration are pressure, solvent type and temperature because they can easily affect their recovery [20].

2.1. Sample Pretreatment

As in most samples derived from plants, an initial pre-treatment step is commonly performed. Specifically, in the case of rosemary and sage plant materials, such as leaves and stems, there is an initial drying step (ambient drying, convection drying, freeze drying, vacuum–microwave drying, radio frequency drying, etc.) for the reduction in moisture and the preservation of the plant material. In the case of sensitive compounds, such as carnosic acid, the drying time and temperature should be taken into account, though ambient drying, convection drying and freeze drying seem to be appropriate and are widely used [3,20]. The drying step is often followed by a milling or grinding step in order to obtain the sample as a fine homogeneous powder [20].

2.2. Conventional Extraction Methods

Plant extracts can be obtained through already well-established conventional techniques, such as maceration, heat reflux or Soxhlet extraction, steam distillation and hydrodistillation [21]. These techniques suffer from numerous disadvantages that include long extraction times, low selectivity of compounds, decomposition of thermolabile compounds and high solvent consumption, especially of non-green solvents such as methanol or hexane [21]. For example, maceration, a simple extraction technique that is frequently employed in literature [22,23], requires a long extraction time in order to be sufficiently effective [24]. Heat reflux extraction techniques such as Soxhlet extraction are also efficient when maintained for several hours [25–32]. Although extractions by heating can be more efficient, compounds readily affected by heat can undergo decomposition, such as the conversion of carnosic acid to carnosol and other derivatives [32]. Such challenges were taken into consideration for the constant improvement of modern methods.

2.3. Ultrasound-Assisted Extraction (UAE)

UAE is a commonly used technique for extracting different compounds from natural sources and was successfully used in the extraction of bioactive constituents from rosemary, sage and other plants [11,33–41]. It is a simple, low-cost technique with short extraction times and reduced solvent consumption, though it offers limited selectivity. In the case of phenolic diterpenes, it is indicated in literature that UAE with aqueous ethanol or methanol is the most efficient, affording higher yields when the solvent polarity decreases [42]. When compared to maceration, UAE proved to be more effective in the extraction of carnosic, rosmarinic and ursolic acids [43,44].

2.4. Microwave-Assisted Extraction (MAE)

MAE is a faster and more environmentally friendly technique relying on microwave volumetric heating, with short extraction times and lower solvent consumption, in comparison to conventional methods. Furthermore, it can be combined with other extraction techniques, such as UAE, and since there is no specific solvent for this type of extraction, any solvent can be chosen according to the target compound as long as it can absorb microwaves [45]. In a recent study, MAE extraction of total phenolics from rosemary afforded a three-fold increase in yield, in comparison to the conventional maceration technique, in a shorter period of time [46]. On the other hand, temperature should be carefully monitored as it was reported that above 150 °C, the content of carnosol increases and is higher than carnosic acid content [47].

2.5. Supercritical Fluid Extraction (SFE)

SFE employs solvents at a supercritical state, taking advantage of their properties, such as low surface tension and viscosity and high solvating capacity. It is a valuable tool for the extraction of bioactive compounds from natural products in high yields and it is environmentally friendly, though appropriate instrumentation can be quite expensive and complex [3]. In particular, supercritical CO_2 offers many advantages in such applications because it facilitates the extraction of sensitive and/or easily oxidized compounds, such as carnosic acid and its derivatives [30,37,48–52]. Pressure is one of the most important parameters regarding this method. Carnosic acid can be extracted using solely supercritical CO_2, not requiring the use of a polar co-solvent [53]. Another advantage of SFE is that it can take place at lower temperatures and in the dark, avoiding the decomposition of carnosic acid during the extraction process [54]. Interestingly, a two-step sequential SFE process can lead to the attainment of rosemary extracts that are enriched in carnosic acid and carnosol. Firstly, neat supercritical CO_2 is employed in order to remove less active fractions, such as waxes and oleoresins, and as a second step, CO_2 is combined with 7% ethanol as a co-solvent. This procedure led to improved recovery for carnosic acid and carnosol in a shortened total extraction time in comparison to the single-step SFE (180 min versus 300 min) [55]. Similarly, semi-preparative supercritical fluid chromatography (SFC) was employed for the fractionation of rosemary extracts, employing an array of SFC-designed columns, operating at different conditions and managing to obtain fractions with carnosic acid concentrations greater than 80% mass [56]. A different method, namely supercritical antisolvent fractionation, is based on the contact between a polar liquid mixture (extract) and a supercritical carbon dioxide current in a pressurized chamber leading to the precipitation of polar constituents, while nonpolar compounds remain in solution [20]. Sánchez-Camargo et al. employed ASE with a mixture of ethanol/water and supercritical antisolvent fractionation in rosemary leaves and reportedly attained highly enriched extracts of carnosic acid and carnosol with potent antiproliferative activity against colon cancer cells HT-29 and HCT116 in vitro [57].

2.6. Accelerated Solvent Extraction (ASE)

The main characteristic of ASE is the use of conventional solvents under high pressure and temperature. Compared to conventional extraction methods, ASE provides rapid extraction and can be used for fractionation of the same extract over time [24]. This type of extraction reportedly afforded rosemary and sage extracts in high yields [30,49–51]. For example, the results obtained in a study employing ASE at high temperatures (200 °C), utilizing water and ethanol as solvents, yielded enriched rosemary extracts after 20 min. Furthermore, under these conditions, two rosemary antioxidants with diverse polarities, carnosic acid and rosmarinic acid, were simultaneously extracted, whereas ASE using ethanol proved more effective for the extraction of carnosic acid and carnosol [58]. When employing solely water as the solvent, this technique can be called subcritical water extraction. Published results indicate a high selectivity for the bioactive compounds of rosemary, i.e., carnosic acid, carnosol, rosmanol and methyl carnosate among others, while the antioxidant activity of different fractions obtained at different water temperatures was comparable to that of SFE-obtained fractions [59].

2.7. Green and Sustainable Solvents

In recent years, new renewable alternatives to volatile organic solvents were developed in order to afford safer extracts with low cost and low toxicity. Such alternatives are ionic liquids and deep eutectic solvents (DES). The former are liquid salts with a melting point below 100 °C, comprised of large cations paired with inorganic or organic anions. They are characterized by their low volatility and flammability [60]. In literature, ionic liquids were combined with eco-friendly extraction techniques, such as MAE and UAE for the extraction of bioactive constituents of rosemary, including carnosic acid [60,61]. In 2011, Liu et al. reported the use of [C_8mim]Br (1-octyl-3-methylimidazolium bromide) under microwave

irradiation, which led to improved extraction yields for carnosic acid and shorter extraction times compared to conventional techniques, such as hydrodistillation [60]. Additionally, Zu et al. utilized the same ionic liquid in UAE of carnosic acid and rosmarinic acid from rosemary while testing an array of anions, demonstrating that the extraction of a particular compound can be dependent on the use of the appropriate anion, influencing the miscibility of the ionic liquid [61].

On the other hand, DESs are liquid mixtures of different compounds formed by a hydrogen bond donor and a hydrogen bond acceptor and exhibiting a melting point that is lower than those of the individual compounds [62]. Natural DESs are specifically composed of naturally derived compounds, e.g., carbohydrates, alcohols, amino acids and organic acids [63]. Regarding the extraction of analytes from rosemary, it was demonstrated that using choline chloride-based DES and UAE or simple stirring with a plethora of hydrogen bond donors can afford higher extraction yields and antioxidant activity in comparison to extraction with ethanol [64,65]. Furthermore, Wang et al. published a study comparing different DESs according to their hydrophobicity, where hydrophobic menthol-based DESs, especially menthol:lactic acid 1:2, were more effective in extracting carnosic acid and carnosol than hydrophilic DESs and organic solvents [66]. Interestingly, the same team later developed a mixture of DES and an ionic liquid with water, which was reportedly effective for the extraction and isolation of carnosic acid from rosemary leaves. In detail, a mixture of choline chloride:laevulinic acid/[BMIM]PF_6/water (1/2/1, *v*/*v*/*v*) was employed, which, when heated, is a single-phase system extracting carnosic acid and rosmarinic acid from rosemary, and when cooled, is switched to a two-phase system with carnosic acid being isolated in the lower phase at a high recovery yield [67]. Finally, a study dedicated to the extraction of bioactive compounds from rosemary with biphasic NADES showcased that a biphasic system consisting of lactic acid:glucose (5:1)/menthol:lauric acid (2:1) separated carnosic acid and carnosol (nonpolar phase) from rosmarinic and caffeic acid (polar phase) [68].

In addition, polyethylene glycols (PEGs) and short-chain alkyl polyethylene glycol ethers were explored as green solvents for the extraction of carnosic acid from rosemary leaves [69,70]. Alkyl polyethylene glycol ethers act as non-ionic hydrotropes, and those with linear alkyl chains and a small molecular volume proved to be suitable for the extraction of carnosic acid from rosemary and provided good yields compared to conventional ionic hydrotropes and an aqueous solution of ethanol [69]. Recently, the use of PEG-400 in MAE extraction of carnosic and rosmarinic acid from rosemary leaves was reported. This solvent was compared to the ionic liquid [C_8mim]Br and ethanol, exhibiting the highest extraction efficiency and fastest extraction rate for the desired compounds [70].

3. Analysis of Carnosic Acid and Carnosol

High-performance liquid chromatography (HPLC) and ultra-high performance liquid chromatography (UHPLC) serve as the most common analytical methods for the separation, identification and quantification of non-volatile compounds from rosemary extracts, such as polyphenols, diterpenes and flavonoids. Characterization of analytes is normally achieved with a suitable detection system, such as a UV diode array detector (DAD) or photodiode array detector (PDA), and in the last two decades, coupled with mass spectrometry (MS) systems [24].

3.1. High-Performance Liquid Chromatography–UV Detection (HPLC–UV)

Chromatographic methods that are discussed below are summarized in Table 2. In literature, there are numerous studies on the characterization of analytes (in most cases carnosic acid, rosmarinic acid and carnosol) from rosemary or sage extracts and their antioxidant activities. The most common methods for the determination of diterpenes, as well as other non-volatile compounds from such extracts, usually employ reverse-phase LC (RPLC) with octadecyl-bonded stationary phases, using both isocratic and gradient mobile phases consisting of different mixtures of water, acetonitrile (ACN) and/or methanol with the addition of acids, with acetic, formic, trifluoroacetic and phosphoric acid being the most prominent [4,5,18,22,25–28,33–36,48,71–81].

Apart from rosemary, sage and other commonly studied species of the Lamiaceae family from the Mediterranean area, more uncommon species were additionally studied through the years. In 2010, the antioxidant and anti-inflammatory activities of the methanol/chloroform (1:1) extracts derived from 16 Salvia species from South Africa were evaluated, indicating good antioxidant activity. Rosmarinic acid, carnosic acid and carnosol were detected as main compounds in the chromatographic profiles, with carnosol being abundant in Salvia namaensis and 7-O-methyl-epirosmanol being detected solely in species S. namaensis and S. chamelaeagnea [76]. Furthermore, different extracts of Dorystoechas hastata, a plant endemic in Turkey, consumed as herbal tea by local inhabitants, were investigated using an HPLC–DAD method, which revealed the presence of carnosic acid and carnosol in the plant. The petroleum ether extract exhibited the most potent antioxidant activity containing the highest amount of carnosic acid and carnosol [77].

Carnosic acid and carnosol are often utilized as food additives in the form of rosemary extracts. Analytical methods for the identification of rosemary extract residues in edible products can be used to verify the safety of such products, for example, a HPLC–PDA quantitative method for the identification of rosemary extract in processed meat products, edible oils and dressings was established, though none of the tested samples contained rosemary extract residues [18]. It is worth noting that recently, an analytical method for the detection of carnosol in human plasma was reported for the first time. In the previous years, there was a lack of data for the pharmacokinetic parameters of carnosol. This HPLC–DAD study provided a sensitive, selective and cost-reduced assay for the evaluation of the clinical effects and safety of carnosol in human plasma [81].

3.2. Liquid Chromatography–Mass Spectrometry (LC–MS)

LC–MS is a highly important analytical technique particularly useful in the analysis of plant extracts, which consists of semi-polar compounds such as key secondary metabolites that can be easily separated and detected by employing LC–MS approaches (Table 3) [23,29–31,36–40,45,49–51,82–92].

In the majority of cases, extracts from fresh or dried rosemary and sage are studied in literature. In the case of commercially available products, the relevant studies are limited. In 2011, a UHPLC methodology with MS/MS and UV detection for the identification and quantification of the main phenolic components in sage tea was described. An Acquity BEH Shield RP18 column was used and the total analysis time was 34 min. A total of 16 commercial brands of sage tea were characterized, and three isomers of rosmanol, in addition to carnosol and carnosic acid, were found and quantified in all samples [85]. In a different study, separation of phenolic diterpenes was attained in 10 min, using a fused-core column. Such columns consist of stationary phases made from high-purity silica that contain a solid core covered with a porous thin layer. This method was applied to five commercial samples consisting of sage leaves, rosemary leaves, a mixture of herbs (rosemary, sage, thyme and oregano), a mixture for chimichurri sauce and oregano leaves. The use of fused-core technology led to good peak shapes, and carnosic acid, rosmanol, carnosol and methyl carnosate were detected and quantified in all samples except oregano leaves [37]. Various analytical methods, including HPLC and UHPLC–MS/MS, were employed for the analysis of rosemary extracts in vitro and fewer in vivo. For example, one of the first studies to investigate the metabolism of carnosic acid in vitro and in vivo employed an HPLC–Q-trap-MS method, resulting in a multiple-ion monitoring information-dependent acquisition-enhanced product ion (MIM-IDA-EPI) mode for the detection of metabolites as traces in biological samples treated with carnosic acid. Different metabolites and degradation products (carnosol, carnosic acid quinone, rosmanol, epirosmanol, rosmadial and 7-oxo rosmanol) were identified from in vitro metabolism models, while glucuronidation, oxidation and methylation were the main in vivo metabolic pathways observed [92]. In a later study, a UHPLC–ESI-MS/MS method was developed, to simultaneously determine carnosic acid, rosmanol, and carnosol in rat plasma after oral administration of rosemary extract to rats. The quantification for this pharmacokinetic study was attained with the use of multiple reaction monitoring (MRM) mode with electrospray ionization (ESI) [88].

Table 2. Summary of reported HPLC–UV analytical methods for the determination of carnosic acid and carnosol.

Analyte	Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–UV	HPLC pump type: 64 (Knauer, Bad Homburg, FRG)	ODS Hypersil column (250 mm × 4 mm, 5 µm, Knauer, Berlin, Germany). The mobile phase consisted of (A) acetonitrile/distilled water/2 M citric acid (51:49:0.83) and (B) acetonitrile/water/2 M citric acid (97:3:0.5); flow rate 0.6 mL/min; temperature 25 °C.	Extraction with methanol containing citric and ascorbic acid (50 ppm); ultrasonication (Sonicator Bandelin sonoplus HD 200 Berlin, Germany, equipped with an MS 73 probe)	[5,33]
Carnosic acid + carnosol	*Salvia officinalis* and *S. fruticosa*, *Origanum onites* and *Origanum indercedens*	HPLC–UV	Varian 9010 HPLC pump, connected to a Varian 9050 UV-vis detector (Mulgrave Victoria, Australia)	Spherisorb ODS 2 (C_{18}) (250 mm × 4.6 mm, 5 µm, Alltech, Deer Field, IL, USA). The mobile phase consisted of (A) 5% (*v*/*v*) acetic acid/acetonitrile 85:15 and (B) methanolic 5% (*v*/*v*) acetic acid; flow rate 1.0 mL/min; temperature 25 °C.	Extraction with methanol	[4]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–DAD	1100 Series (Agilent Technologies, Waldbronn, Germany)	Zorbax SB-C_{18} (150 mm × 3 mm, 3.5 µm, Zorbax, Agilent Technologies, Palo Alto, CA, USA). The mobile phase consisted of (A) 400 mL water 600 mL acetonitrile, 1.5 mL trifluoroacetic acid and (B) 1000 mL MeOH, 1.5 mL TFA; flow rate 0.42 mL/min; temperature 45 °C.	Commercially available rosemary extract (powder)	[48]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–DAD	Hewlett-Packard HP 1100 equipped with a diode array detector (Agilent, Palo Alto, CA, USA)	C_{18} LiChrospher 100 analytical column (250 mm × 4 mm, 5 µm, Merck, Darmstadt, Germany). The mobile phase consisted of (A) water with 1% acetic acid and (B) methanol; flow rate 1.0 mL/min; temperature 30 °C.	Extraction with DMSO	[72]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–UV	HPLC equipped with a Gilson Holochrome UV detector (Gilson Incorporated, Middleton, WI, USA)	C_{18} Hypersil-ODS column (250 mm × 4.6 mm, 5 µm, Supelco, Dorset, England). The mobile phase consisted of (A) deionized wateR, acetic acid and acetonitrile and (B) methanol; flow rate 1.5 mL/min; temperature 25 °C.	Extraction with dichloromethane and ethanol 75:25 *v*/*v*)	[73]

Table 2. *Cont.*

Analyte	Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–DAD	Merck-HITACHI LaChrom system combined with a L-7100 pump and a Merck-HITACHI photodiode array detector DAD L-7450 (Tokyo, Japan)	Merck Chromolith Performance RP-18e, (100 mm × 4.6 mm, 5 µm). The mobile phase consisted of (A) acetate buffer pH 3.5 and (B) methanol; flow rate 1.5 mL/min; temperature 25 °C.	Extraction with methanol	[74]
Carnosic acid + carnosol	*Salvia rosmarinus* L. and *Salvia officinalis* L.	HPLC–UV	Waters 600 Controller, 2487 Dual λ Absorbance Detector, 717plus Autosampler (Milford, MA, USA)	Nucleodur column 100-5 C18ec, (125 mm × 2 mm, 5 µm, Macherey-Nagel, Duren, Germany). The mobile phase consisted of (A) acetonitrile–water–phosphoric acid (65.1%:34.9%:0.02%) and (B) acetonitrile–water–phosphoric acid (22%:78%:0.25%); flow rate 0.5 mL/min; temperature 25 °C.	Extraction with 80% ethanol	[75]
Carnosic acid + carnosol	*Salvia officinalis* L. and *Salvia rosmarinus* L.	HPLC–DAD	Hewlett-Packard system with a G1311A quaternary pump and G1315A photodiode array UV-vis detector (Palo Alto, CA, USA)	Zorbax SB-C18 column (250 mm × 4.6 mm, 5 µm, Hewlett-Packard). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 5% formic acid%); flow rate 1.0 mL/min; temperature 25 °C.	Soxhlet extraction with methanol (B-811, Buchi, Flawil, Switzerland)	[25–28]
Carnosic acid + carnosol	16 South African *Salvia* species	HPLC–DAD	Waters 2695 HPLC system (Waters Corporation, Milford, MA, USA) with a 2996 photodiode array detector	Phenomenex Aqua C18 column (250 mm × 2.1 mm, 5 µm, Phenomenex, Torrance, CA, USA). The mobile phase consisted of (A) 10% acetonitrile and (B) 90% water containing 10 mM formic acid; flow rate 0.2 mL/min; temperature 40 °C.	Extraction with methanol:chloroform (1:1)	[76]
Carnosic acid + carnosol	*Dorystoechas hastata* L.	HPLC–DAD	Agilent 1100 series HPLC instrument equipped with an autosampler and a diode array detector (Agilent, Palo Alto, CA, USA)	Hypersil ODS C18 type (250 mm × 4.6 mm, 5 µm). The mobile phase consisted of (A) 5% acetic acid in water and (B) methanol; flow rate 0.9 mL/min; temperature 28 °C.	Extraction under reflux with methanol, water, acetone, ethyl acetate or petroleum ether	[77]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–DAD	Agilent 1200 series autosampler, pump, diode array detector (Agilent, Palo Alto, CA, USA)	Cyclobond I 2000 RSP column (250 mm× 4.6 mm, 5 µm).The mobile phase consisted of (A) 70% water, 30% acetonitrile, 0.1% formic acid and (B) 40% water, 60% acetonitrile and 0.1% formic acid.	Commercially available	[78]
Carnosic acid	*Lippia alba*, *Lippia origanoides*, *Lippia micromera*, *Lippia americana*, *Lippia graveolens* and *Lippia citriodora*	HPLC–DAD	Agilent Technologies 1200 LC, with a quaternary pump (AT G1353A), a manual injector (G1328B), and a UV-Vis DAD (G1315B) (Agilent, Palo Alto, CA, USA)	ZORBAX Eclipse XDB-C18 (150 mm × 4.6 mm, 5 µm). The mobile phase consisted of (A) *o*-phosphoric acid aqueous solution (0.1%) and (B) methanol; flow rate 1.0 mL/min; temperature 35 °C.	Extraction with aqueous methanol and supercritical fluid extraction (Thar SFE-2000–2-FMC50, Thar Instruments, Pittsburgh, PA, USA)	[48]

Table 2. *Cont.*

Analyte	Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–DAD	Waters LC (Milford, MA, USA) with a Model 600 pump and a Model 600 gradient controller, connected to a Model 717 autosampler and a Model 996 photodiode-array detector.	Chromolith Performance RP-18e (100 mm × 4.6 mm I.D, VWR International, Radnor, PA, USA).The mobile phase consisted of (A) water/formic acid (99.5/0.5) and (B) acetonitrile; flow rate 4.0 mL/min.	Extraction with methanol/water (80:20, *v*/*v*)	[79]
Carnosic acid	*Origanum sipyleum* L.	HPLC–DAD	SCL-10 Avp System controller (Shimadzu Scientific Instruments, Columbia, MD), SIL–10AD vp Autosampler (Shimadzu), LC–10AD vp pump, DGU-14a degasser (Shimadzu), CTO-10 Avp column heater (Shimadzu) and a diode array detector	Zorbax Agilent Eclipse XDB (250 mm × 4.6 mm, 5 µm, Agilent Part No. 990967-902, Palo Alto, CA). The mobile phase consisted of (A) acetic–water (2:98, *v*/*v*) and (B) methanol; flow rate 0.8 mL/min; temperature 30 °C.	Extraction with methanol. Ultrasonication (Super RK 255 H, Bandelin Electronic, Berlin, Germany)	[34]
Carnosic acid	41 populations from 27 Iranian *Salvia* species	HPLC–UV	Smartline HPLC (Kenuer, Germany) with a quaternary pump and a UV-VIS detector (D-14163 model)	C18 Eurospher-100 (125 mm × 4.6 mm, 5 µm). The mobile phase consisted of (A) 0.2% (*v*/*v*) glacial acetic acid in water and (B) acetonitrile; flow rate 1.0 mL/min.	Maceration in methanol	[22]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–DAD	Hewlett-Packard HP 1100 with a diode array detector (Palo Alto, CA, USA)	C18 LiChrospher 100 analytical column (250 mm × 4.6 mm, 5 µm, Merck, Darmstadt, Germany). The mobile phase consisted of (A) acetonitrile and (B) water, phosphoric acid (0.2%); flow rate 0.75 mL/min; temperature 30 °C.	Commercial extracts	[80]
Carnosic acid	*Salvia miltiorrhiza* Bunge	HPLC–DAD	Waters Acquity UPLC H-class with a quaternary solvent manager and a photodiode array detector (Waters Co., Milford, MA, USA)	Waters Acquity UPLC BEH Shield RP18 Column (150 mm × 3 mm, 1.7 µm, Waters, USA). The mobile phase consisted of (A) acetonitrile and (B) water with 0.01% (*v*/*v*) formic acid%; flow rate 0.5 mL/min.	Extraction with 80% aqueous methanol. Ultrasonication (Scientz SB-5200DTD ultrasonic instrument, Ningbo, China)	[35]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–DAD	Agilent Technologies 1260 series Infinity System LC (Santa Clara, CA, USA), with a photodiode-array detector, a 1260 quaternary pump VL, and an AT-330 thermostatted column compartment	Agilent Poroshell 120 EC-C18 column (150 mm × 4.6 mm, 4 µm, Wilmington, NC, USA). The mobile phase consisted of (A) acetonitrile and (B) 0.1% aqueous phosphoric acid (*v*/*v*); flow rate 1.0 mL/min; temperature 30 °C.	Extraction with ethanol Ultrasonication (KQ3200DE, Kunshan Ultrasonic Instrument Co., Ltd., Jiangsu, China)	[36]

Table 2. *Cont.*

Analyte	Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Carnosic acid	*Thymus zygis* ssp. gracilis	HPLC–DAD	Hewlett Packard system (Germany) with a G1311A quaternary pump and G1315A photodiode array UV-vis detector	ZORBAX SB-C18 column (250 mm × 4.6 mm, 5 µm, Hewlett Packard, Palo Alto, CA, USA). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 5% formic acid; flow rate 1.0 mL/min.	Soxhlet extraction with methanol (B-811) (Buchi, Flawil, Switzerland)	[28]
Carnosic acid + carnosol	Food samples	HPLC–DAD	Waters 2695 separation module HPLC system (Waters Co., Milford, MA, USA) with a pump, an autosampler, a column oven, and a 996 photodiode array detector	Shiseido Capcell Pak C18 UG120 (4.6 mm × 250 mm, 5.0 µm, Shiseido, Tokyo, Japan). The mobile phase consisted of (A) methanol and (B) 1% acetic acid in water; flow rate 1.0 mL/min; temperature 30 °C.	Extraction with n-hexane-saturated acetonitrile	[18]
Carnosol	Human plasma	HPLC–DAD	Shimadzu (Tokyo, Japan) LC 20 with a LC20AT pump, SIL AH-HT autosampler part, a SPD-20A HT UV detector and CTO 10 AC column oven	C18 column (150 mm × 4.6 mm, 5 µm, ShimPack, Shimadzu Corporations, Tokyo, Japan). The mobile phase consisted of (A) methanol and (B) 2% aqueous o-phosphoric acid (*v*/*v*); flow rate 1.2 mL/min; temperature 25 °C.	Extraction with n-hexane	[81]

Table 3. Summary of reported LC–MS analytical methods for the determination of carnosic acid and carnosol.

Analyte	Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–ESI-MS (positive + negative mode)	Agilent 1100 series LC/MSD ion trap (Agilent Technologies, Waldbronn, Germany).	Ultrabase C-18 (250 mm × 4.6 mm, 5 µm, Scharlau, Barcelona, Spain). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 0.1% formic acid.	Extraction with methanol	[83]

Table 3. *Cont.*

Analyte	Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Carnosic acid + carnosol	*Salvia rosmarinus* L.	UPLC–MS/MS (ESI negative mode)	Accela liquid chromatograph (Thermo Scientific, San Jose, CA, USA) equipped with a DAD and an autosampler coupled to a TSQ Quantum triple quadrupole analyzer (Thermo Scientific, San Jose, CA, USA)	Hypersil Gold column (50 mm × 2.1 mm, 1.9 µm, Thermo Scientific). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 0.1% formic acid; flow rate 0.4 mL/min.	Supercritical fluid extraction (Thar Technology, Pittsburgh, PA, USA, model SF2000); accelerated solvent extraction (ASE 200, Dionex, Sunnyvale, CA, USA); water extraction and particle formation on-line (WEPO)	[49]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–DAD-ESI-TOF-MS (positive + negative mode)	Agilent 1200 Series Rapid Resolution LC system (Agilent Technologies, Palo Alto, CA, USA) coupled to a microTOFTM (Bruker Daltonik, Bremen, Germany), an orthogonal accelerated TOF mass spectrometer (oaTOFMS), with an ESI interface (model G1607A from Agilent Technologies, Palo Alto, CA, USA)	Zorbax Eclipse Plus C18 (150 mm × 4.6 mm, 1.8 µm, Agilent Technologies, Palo Alto, CA, USA). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 0.1% formic acid; flow rate 0.8 mL/min.	Supercritical fluid extraction (Suprex Prep Master, Suprex Corporation, Pittsburg, PA, USA). Accelerated solvent extraction (ASE 200, Dionex, Sunnyvale, CA, USA)	[50]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC/DAD/MS (positive + negative mode)	HP 1100L LC with a DAD detector and a HP 1100 MSD mass spectrometer with an API/electrospray interface (Agilent Technologies, Palo Alto, CA, USA)	Fusion, RP18 column (150 mm × 3.9 mm, 4 µm, Phenomenex, USA). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 0.1% formic acid; flow rate 0.8 mL/min; temperature 26 °C.	Extraction with ethanol	[84]
Carnosic acid + carnosol	*Salvia officinalis* L. (commercially available sage tea)	UHPLC–UV-MS (negative mode)	Acquity UPLC (Waters, Milford, MA, USA) and a triple quadrupole mass spectrometer (Acquity TQD) with electrospray interface	Acquity BEH Shield RP18 column (150 mm × 2.1 mm, 1.7 µm, Waters). The mobile phase consisted of (A) acetonitrile and (B) water both acidified with 0.1% (*v*/*v*) formic acid; flow rate 0.4 mL/min.	Infused with boiling water	[85]
Carnosic acid + carnosol	*Salvia rosmarinus* L. and *Salvia officinalis* L.	LC/DAD/ESI-MS^n (negative mode)	MSD trap SL quadrupole ion trap mass analyzer (Agilent Technologies) and a 1100 binary HPLC with a degasser, autosampler, diode array detector and ESI source (Agilent Technologies, Karlsruhe, Germany)	Altima C18 analytical column (250 mm × 4.6 mm, 5 µm, Alltech, Deerfield, USA). The mobile phase consisted of (A) acetonitrile and (B) (water/acetic acid, 99.9: 0.1 *v*/*v*); flow rate 0.6 mL/min.	Soxhlet extraction with ethyl acetate	[29]
Carnosic acid	*M. piperita*, *O. vulgare*, *S. rosmarinus* L. and *T. vulgaris* L.	HPLC–ESI/MS/MS (negative mode)	HPLC Thermo Finnigan Spectra System UV 6000 LP coupled to a quadrupole MS: Finnigan TSQ Quantum Discovery equipped with an electrospray ionisation interface Thermo Scientific (Olten, Switzerland)	Kinetex™ XB-C18 100 Å, LC Column (100 mm × 4.6 mm, 2.6 µm, Phenomenex, Macclesfield, UK). The mobile phase consisted of (A) methanol and (B) acidified water containing 0.1% formic acid; flow rate 1.0 mL/min.	Soxhlet extraction (Behrotest®, Düsseldorf, Germany); accelerated solvent extraction (Dionex ASE 350 from Vertex Technics, Barcelona, Spain); supercritical fluid extraction (Thar process, Pittsburgh, PA, USA)	[30]

Table 3. *Cont.*

Analyte	Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–ESI-QTOF-MS (negative mode)	UPLC Acquity (Waters, Millford, MA, USA) with a microTOF-Q II mass spectrometer (Bruker Daltoniks, Bremen, Germany) and an ESI interface (Bruker Daltoniks, Bremen, Germany)	Zorbax Eclipse Plus C18 (4.6 mm × 150 mm, 1.8 µm). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 0.1% formic acid; flow rate 0.8 mL/min; temperature 4 °C.	Microwave-assisted extraction with methanol-water 70:30 (*v*/*v*) (microwave oven, LG Electronics, Seoul, Republic of Korea)	[45]
Carnosic acid + carnosol	*Salvia officinalis* L. *Salvia rosmarinus* L. mixture of herbs (sage, oregano, thyme and rosemary), mixture for chimichurri sauce and *Origanum vulgare* L.	UPLC–MS (negative mode)	UPLC–MS (Waters, Milford, MA, USA) with a single quadrupole mass detector	Acquity, UPLC BEH C18, (50 mm × 2.1 mm, 1.7 µm, Waters, Milford, USA). The mobile phase consisted of (A) acetonitrile with 0.1% (*v*/*v*) of acetic acid and (B) acidified water with 0.1% (*v*/*v*) of acetic acid; flow rate 0.8 mL/min; temperature 55 °C.	Supercritical fluid extraction and extraction with ethanol assisted by ultrasonication (Unique, Indaiatuba Brazil)	[37]
Carnosic acid	*Salvia rosmarinus* L.	LC–ESI-MS/MS (negative mode)	Agilent 1200 series HPLC tandem triple quadrupole API 3200 mass spectrometer (Applied Biosystems, Foster City, CA, USA)	Agilent Eclipse PlusC18column (150 mm × 4.6 mm, 5 µm) The mobile phase consisted of (A), formic acid in water (0.1%, *v*/*v*), and (B), formic acid in methanol (0.1%, *v*/*v*); flow rate 0.8 mL/min; temperature 35 °C.	Maceration with ethanol	[23]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–PDA/ESI-MS (positive and negative mode)	1525 binary HPLC pump, PDA 996 photodiode array detector and Micromass ZQ mass analyzer with a ESI Z-spray source (Waters Italia S.p.A., Milan, Italy)	Luna C18 RP column (250 mm × 4.6 mm, 5 µm, Phenomenex Italia). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 2.5% formic acid; flow rate 1.0 mL/min; temperature 25 °C.	Extraction with ethyl acetate and ethanol	[86]
Carnosic acid	*Himanthalia elongata* (Irish seaweed)	LC–DAD–ESI-MS/MS (negative mode)	Agilent Technologies 6410 Triple Quadrupole LC/MS with Agilent 1200 series LC, G1315B DAD (Agilent Technologies, Santa Clara, CA, USA)	Atlantis C-18 (250 mm × 4.6 mm, 5 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) acetonitrile/water and (B) 0.25% aqueous acetic acid; flow rate 1.0 mL/min; temperature 25 °C.	Extraction with 60% (*v*/*v*) methanol in water	[87]
Carnosic acid + carnosol	*Salvia rosmarinus* L.. in rat plasma samples	UHPLC–ESI-MS/MS (negative mode)	UHPLC–MS 1290 series (Agilent Technologies, Santa Clara, CA, USA)	C18 column ACQUITY UPLC HSS T3 (100 mm × 2.1 mm, 1.8 µm) The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 0.1% formic acid; flow rate 0.3 mL/min.	Extraction with ethanol water 80:20 (*v*/*v*)	[88]
Carnosic acid + carnosol	*Salvia* spp. plants	UPLC–MS (negative mode)	Waters Acquity UPLCTM H-Class (Waters, Milford, MA) with Xevo TQ-S tandem quadrupole mass spectrometer (Waters, Milford, MA, USA)	Acquity BEH C18 column (100 mm × 2.1 mm, 1.7 µm, Waters, Milford, MA, USA). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 0.1% formic acid; flow rate 0.4 mL/min; temperature 40 °C.	Supercritical fluid extraction (Helix extraction system, Applied Separation, PA, USA). Ethanol/water accelerate solvent extraction (Dionex ASE 350, Sunnyvale, CA, USA)	[51]

Table 3. *Cont.*

Analyte	Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–DAD-ESI-MS (positive mode)	Agilent 1200 HPLC Series system (Agilent Technologies, Santa Clara, CA, USA) with a diode array (DADG1315D) and a single quadrupole mass spectrometer (Agilent Technologies 6110 system, Santa Clara, USA)	Zorbax Eclipse XDBC18 column (4.6 mm × 150 mm, 5 µm). The mobile phase consisted of (A) water:acetonitrile:acetic acid (99:0.9:0.1, *v*/*v*/*v*) and (B) acetonitrile:acetic acid (99.9:0.1, *v*/*v*); flow rate 0.5 mL/min; temperature 25 °C.	Extraction with aq. methanol 95% containing 1% HCl (aq.), Ultrasonication (XUB5 model)	[36]
Carnosic acid + carnosol	*Salvia pomifera* L. *Salvia fruticosa Mill.*	LCz-Q/TOF-MS/MS (positive and negative mode)	Dionex Ultimate 3000RS HPLC (ThermoScientific, California, CA, USA) with a Bruker MicrOTOF-Q II mass spectrometer (Bruker Daltonics, Bremen, Germany)	Dionex Acclaim 120 C8 column (2.1 mm × 150 mm, 5 µm, ThermoScientific, California, CA, USA). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 0.1% acetic acid; flow rate 0.3 mL/min; temperature 23 °C.	Soxhlet extraction with methanol	[31]
Carnosic acid + carnosol	Naked barley flours	LC–MS-IT-TOF (positive and negative mode)	LC–MS-IT-TOF (ABT4700, USA)	Shimadzu Shim-pack VP-ODS column (150 mm × 2.0 mm, 5 µm). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 0.1% formic acid; flow rate 1.0 mL/min.	Extraction with aq. methanol (80%) Ultrasonication (KQ-500DE, Kunshan, Jiangsu, China)	[38]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	UPLC–Orbitrap-MS/MS (positive and negative mode)	Thermo Vanquish Flex Binary RSLC platform (Thermo Fisher Scientific, Waltham, MA, USA) Q-Exactive Plus Orbitrap mass spectrometer (Thermo Scientific, Waltham, MA, USA)	Hypersil GOLD aQ C18 column (100 mm × 2.1 mm, 1.9 µm, Thermo Fisher, Waltham, MA, USA) The mobile phase consisted of (A) methanol and (B) acidified water containing 0.1% formic acid; flow rate 0.3 mL/min; temperature 40 °C.	Extraction with aq. ethanol	[89]
Carnosic acid + carnosol	*Salvia rosmarinus* L. *Salvia officinalis* L.	HPLC–PDA-MS (positive and negative mode)	LC-PDA-MS Thermo Finnigan (LC Pump Plus, Autosampler, Surveyor PDA Plus Detector) with an ESI MSQ Plus (Thermo Finnigan, MA, USA)	SB-Aq RP-C18 column (150 mm × 3 mm, 5µm, Agilent Agilent Technologies, Palo Alto, CA, USA). The mobile phase consisted of (A) acetonitrile and (B) water-0.05% formic acid; flow rate 0.4 mL/min.	Extraction with methanol	[90]
Carnosic acid	*Premna microphylla* Turcz.	UPLC–LTQ-Orbitrap-MS (positive and negative mode)	Hypersil GOLD Thermo Scientific HPLC system (Thermo Fisher Scientifc, Waltham, MA, USA) coupled to a LTQ mass Spectrometer	Thermo Hypersil Gold Column (100 mm × 2.1 mm, 1.9 µm). The mobile phase consisted of (A) acetonitrile and (B) acidified water containing 0.075% formic acid; flow rate 0.2 mL/min.	Extraction with methanol. Ultrasonication (AnonKia Shenzhen Guan Yijia Technology Co., Ltd., Guangdong, China)	[39]
Carnosic acid + carnosol	*Salvia fruticosa* and *S. pomifera* subsp. Calycina *S. pomifera* subsp. pomifera	UHPLC–DAD-ESI-MS (positive and negative mode)	Dionex UltiMate 3000 LC (Thermo Fisher Scientific, Waltham, MA, USA) with a quadrupole ion-trap Bruker amaZon SL MS (Bruker Daltonics, Billerica, MA, USA)	Acclaim 120 C18 (2.1 mm × 100 mm, 3 µm, Thermo Fisher Scientific, Waltham, MA, USA). The mobile phase consisted of (A) 0.2% (*v*/*v*) formic acid in water and (B) 0.2% (*v*/*v*) formic acid in acetonitrile; flow rate 0.3 mL/min; temperature 35 °C.	Extraction with methanol and ultrasonication	[40]

Table 3. *Cont.*

Analyte	Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Carnosic acid + carnosol	*Salvia rosmarinus* L.	LC–DAD-ESI-MS (negative mode)	Shimadzu LC/MS-2010A with a LC–10ADvp binary pump, a DGU-14A degasser, a SIL-10ADvp autosampler, and a SPD-M10Avp Photo Diode Array Detector (Shimadzu, Tokyo, Japan)	Discovery HS-C18 column (4.6 mm × 250 mm, 5 µm, Supelco, Bellefonte, PA, USA) The mobile phase consisted of (A) 0.1% (*v*/*v*) formic acid in water at pH 2.5 and (B) methanol; flow rate 0.4 mL/min; temperature 25 °C.	Clevenger hydrodistillation and UAE with ethanol (Sonorex Super RK 255H type, Bandelin Electronic, Berlin, Germany)	[91]
Carnosic acid	Subcellular fractions from human and rats, *C. elegans* culture, Rat urine and feces	LC–UV-MS/MS (positive and negative mode)	Agilent series 1200SL (Agilent Technologies, USA) with a vacuum degasser, a binary pump, an autosampler and a diode array detector coupled to an ABSciex API 4500 Q-Trap mass spectrometer (Foster City, CA, USA) with a Turbo VTM ion source	Zorbox Extend-C18 column (100 mm × 2.1 mm, 3.5 µm, Agilent, USA). The mobile phase consisted of (A) 0.1% (*v*/*v*) formic acid in water and (B) 0.1% (*v*/*v*) formic acid in acetonitrile; flow rate 0.4 mL/min; temperature 30 °C.	Extraction with acetonitrile (in vitro samples) Agilent Accubond II ODS-C18 solid phase extraction cartridges (Agilent Technologies, USA) water/methanol (in vivo samples)	[92]

3.3. Capillary Electrophoresis (CE) and Other Techniques

CE with UV or MS detection was also used for the separation of diterpenes from rosemary and sage extracts [58,93–96] (Table 4). Silica capillaries of 50 cm length were the most commonly used and the pH was maintained between 9 and 10, in favor of the anionic phenolic compounds. When coupled to MS, ammonium acetate was used as a buffer replacing sodium borate or tetraborate, due to their incompatibility with ESI-MS detection as a result of low volatility [58].

Table 4. Summary of capillary electrophoresis and other reported analytical methods for the determination of carnosic acid and carnosol.

Analyte	Origin	Analytical Technique	Instrumental Analysis	Column/Mobile Phase	Sample Preparation—Solvent Extraction	Ref.
Carnosic acid	*Salvia rosmarinus* L.	HPCE–UV-DAD	Beckman CE instrument P/ACE 5500 (Beckman Instruments, Inc., Fullerton, CA, USA) with a diode array detector	50 µm ID × 375 µm OD (Beckman); 47 cm total capillary length; running buffer 20 mM sodium tetraborate (pH 9.0); temperature 35 °C.	Extraction with methanol, chloroform, isopropyl alcohol and 1:1 methanol: chloroform	[93]
Carnosic acid	*Salvia rosmarinus* L.	CE–ESI–MS (negative mode)	CE apparatus (P/ACE5500, Beckman Instruments, Fullerton, CA, USA) with a UV-vis detector and coupled to an ion-trap mass spectrometer (Esquire 2000, Bruker Daltonik, Bremen, Germany) with an orthogonal ESI (model G1607A, Agilent Technologies, Palo Alto, CA, USA)	Fused-silica capillary µm ID (Composite Metal Services, Worcester, UK). Length to the UV detector was 20 cm; running buffer 40 mM ammonium acetate/ammonium hydroxide (pH 9.0).	ASE with water (200 system, Dionex, Sunnyvale, CA, USA)	[58]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	SFC-UV	Supercritical fluid chromatography pilot plant (Thar Designs, USA) coupled to a UV/vis detector UV 1000 model (San Jose, CA, USA)	25 cm × 10 mm ID Supelco SIL LC–Diol packed column, 5 µm (Supelco, Bellefonte, PA, USA); CO_2 flow rate 20 g/min.	Supercritical fluid extraction (Iberfluid, Spain)	[52]
Carnosic acid	*Salvia officinalis* L. (Commercially available tea bags)	CE-DAD	Agilent CE system with a diode-array detector (Agilent, Palo Alto, CA, USA)	Capillary 50 µm ID (Polymicro Technologies, Phoenix, AZ, USA); 53 cm total capillary length; running buffer sodium tetraborate (pH 9.6).	Infused with boiling water	[94]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPCE-DAD	P/ACE MDQ capillary electrophoresis instrument (Beckman, CA, USA) equipped with a diode array detector	Fused silica capillary (75 µm × 57 cm, Yongnian Fibre Factory, China). Effective length 50 cm; running buffer 12 mmol/L borax and 20% methanol (pH 9.9).	Extraction with methanol	[95]
Carnosic acid	14 *Salvia* species from Anatolia	CE	Agilent 1600 capillary electrophoresis system (Waldbronn, Germany)	Silica capillaries (50 µm_m i.d., Polymicro Technology, Phoenix, AZ, USA). Capillary length 67 cm; running buffer 20 mM borate (pH 9.6).	Extraction with methanol	[96]
Carnosic acid + carnosol	*Salvia rosmarinus* L.	HPLC–ELSD (evaporative light scattering detection)	SCL-10Avp HPLC (Shimadzu, Kyoto, Japan), LC–10ATvp pumps (Shimadzu), CTO-10ASvp column oven (Shimadzu) coupled to a SofTA Model 400 ELSD (SofTA Corporation, Boulder, CO, USA)	Zorbax SB-C18 column (4.6 mm × 250 mm, 5 µm, Agilent, Palo Alto, CA, USA). The mobile phase consisted of (A) methanol and (B) 0.6% acetic acid in water; flow rate 1.0 mL/min; temperature 30 °C.	Extraction with methanol. Ultrasonication (KQ-5200DE, Kun Shan Ultrasonic Instruments Co., Ltd., Jiangsu, China)	[41]
Carnosic acid + carnosol	*Salvia officinalis* L.	GC-MS	GC coupled to a mass spectrometer (Shimadzu GCMS QP 2020, Shimadzu, Kyoto, Japan)	Zebron ZB-5 MSi capillary column (30 m × 0.25 mm, 0.25 µm; Phenomenex, Torrance, CA, USA). The carrier gas was helium at a flow rate of 1.02 mL/min.	Extraction with 2 M sodium hydroxide and ethyl acetate. Derivatization with N,O-bis-(trimethylsilyl)trifluoroacetamide (BSTFA)	[97]
Diterpene acids	*Salvia officinalis* L.	UV	LAMDA 25 spectrophotometer (Perkin Elmer, United States)	-	Extraction with petroleum ether 40/70	[98]
Carnosic acid	*Salvia rosmarinus* L.	SWV	IviumStat electrochemical analyzer (Potentiostat/Galvanostat, The Netherlands)	-	Maceration with ethanol	[99]

It is worth noting that an analytical method was also reported involving HPLC with evaporative light scattering detection (HPLC–ELSD), for the determination of rosmarinic acid, carnosol and carnosic acid, among other analytes, in rosemary, in a cost- and time-effective manner. The drift tube temperature of ELSD was set at 70 °C, and the pressure of the nebulizer nitrogen gas was set at 40 Psi. This method showcased satisfactory sensitivity (limits of detection from 1.3 to 8.6 μg/mL), good repeatability and high accuracy (recovery between 95.5% and 100.8%) [41].

Two less-explored techniques that were applied for the analysis of diterpenes such as carnosic acid are UV spectrophotometry and square-wave voltammetry (SWV) [98,99]. The former was utilized for the quantitative determination of the diterpenes extracted from garden sage leaves. The measured concentrations of diterpenes at 285 nm, ranged from 2.1 to 3.6% in terms of carnosic acid [98]. Yilmaz et al. studied the electrochemical behavior of carnosic acid and based on their findings, developed a square-wave voltammetric method for the determination of carnosic acid in rosemary extracts. This method displayed good linear responses and the results are in good agreement with an HPLC–UV method [99].

4. Biological Activities of Carnosic Acid and Carnosol

4.1. Antioxidant Activity

The in vitro antioxidant activity of rosemary and sage extracts was extensively studied in literature through the use of spectrophotometric methods, including 2,2-diphenyl-1-picrylhydrazil (DPPH) and 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays [32]. The specific antioxidant activities of carnosic acid and carnosol were demonstrated via oxidation reactions and by protecting cells from oxidative cell death. For example, carnosic acid can provide protection of neuronal cells against oxidative stress caused by the presence of hydrogen peroxide and lipid hydroperoxides in those circumstances [100].

4.2. Anticancer Activity

The anticancer activity of rosemary extracts and their major bioactive constituents were widely studied in the last decades [101–106]. Numerous studies employing in vitro assays regarding different types of cancer, such as leukemia, breast, lung, liver, brain, prostate and colon cancer were conducted. The anticancer activity of rosemary extracts is characterized as chemopreventive, antiproliferative and anti-invasive according to its effect against the different stages in the development of cancer [101–106].

Carnosic acid was demonstrated to inhibit angiogenesis, proliferation and migration of cancer cells [107,108]. Moreover, it induced cell apoptosis and DNA damage and was able to inhibit the mitogen-activated protein kinase (MAPK) signaling pathways [109]. Additionally, carnosic acid can inhibit the growth, cell migration and invasion of human non-small cell lung carcinoma cells (A549) via apoptosis and suppression of the PI3K/AKT/m-TOR signaling pathway [110]. Importantly, studies on carnosic acid reported its ability to enhance the effects of different drugs; for example, trastuzumab [111] and temozolomide [112]. A new study reported that carnosic acid displays cytotoxic activity against human gastric cancer cells [113]. Finally, carnosic acid inhibited the tumor growth in BALB/c nude mice transplanted with oral squamous cell carcinoma (OSCC) cells [114].

Carnosol was reported to inhibit prostate and breast cancers by binding to estrogenic as well as androgenic receptors [115] and to exert its effect against breast cancer through downregulation of matrix metallopeptidase 9 (MMP-9) and inhibition of the signal transducer and activator of transcription 3 (STAT3) signaling pathway [116].

4.3. Anti-Inflammatory Activity

Rosemary extracts, in particular, their components carnosic acid and carnosol, exhibited a plethora of anti-inflammatory properties against lung, skin, cardiac, gut, renal, neuronal, endothelial diseases as well as diabetes- and obesity-associated inflammatory diseases [117]. Carnosic acid and carnosol displayed significant in vivo anti-nociceptive and anti-inflammatory effects dose-dependently in carrageenan-induced mouse hyperalgesia

and induced inhibition of the analgesic response in the late phase of the formalin test [118]. Xia et al. reported that the administration of carnosic acid to *db/db* mice led to a reduction in the risk of systemic inflammatory conditions [119], while carnosol and rosmanol alleviated rheumatoid arthritis in a synergistic manner by inhibiting inflammation through regulation of the TLR4/NF-κB/MAPK pathway [120]. Carnosic acid showed osteoarthritis prevention due to its ability to reduce cartilage degeneration in articular chondrocytes [121]. In a bleomycin-induced lung damage animal model, carnosol reduced the levels of oxidative markers and pro-inflammatory cytokines [122].

4.4. Neuroprotective Activity

Accumulating evidence shed light on the relevance of carnosic acid as a neuroprotective agent that exhibits therapeutic efficacy against neurodegenerative disorders [100,123]. A recent review article by Satoh et al. summarizes the ability of carnosic acid to act as a nuclear factor erythroid 2-related factor 2 (NRF2) activator and to inhibit the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which was linked to neurological diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) [84]. In vivo protection by carnosic acid was explored in PD models employing 6-hydroxydopamine (6-OHDA) to cause injuries to the dopaminergic neurons in the substantia nigra. Carnosic acid treatment ameliorated the locomotor activity of rats exposed to 6-OHDA and protected them against lipid peroxidation [124].

5. Conclusions

Carnosic acid and carnosol are two very important natural products, which are found in plants belonging to the Lamiaceae family. Both are phenolic diterpenes, exhibiting very attractive biological properties, namely antioxidant, anticancer, anti-inflammatory and neuroprotective activities. Due to their bioactivities and their applications as antioxidant food additives, a variety of analytical methods were developed for their determination. These methods, which include HPLC–UV, LC–MS and CE techniques, are summarized in the present review article. In addition, the various extraction methods of these bioactive phytochemicals from the plant sources are discussed. Future research should consider further focus on the development of robust analytical methodologies for the determination of carnosic acid, carnosol as well as their derivatives on a broader spectrum of samples (foods, plants and biological samples) and to take advantage of their pleiotropic biological activities as individual compounds and as constituents of rosemary and sage extracts.

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