Rosmarinic Acid – Pharmaceutical and Clinical Aspects

Authors

Solomon K. S. Amoah, Louis P. Sandjo, Jadel M. Kratz, Maique W. Biavatti

Affiliation

Postgraduate Program in Pharmacy, Universidade Federal de Santa Catarina – UFSC, Florianópolis, SC, Brazil

Key words

- rosmarinic acid
- isolation and analysis
- clinical studies
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Abstract

The biosynthesis and biotechnological production of Rosmarinic acid, a phenolic ester that is widespread in the plant kingdom, has been widely investigated. This compound has shown many remarkable biological and pharmacological activities, which have led to its pharmaceutical and analytical development, as well as clinical studies, which are summarized and analyzed here for the first time. This review compiles data from the Pubmed, Scopus, Scifinder, Web Of Science, and Science Direct databases published between 1990 and 2015, restricting the search to works with the keywords “Rosmarinic acid” in the title. The initial search identified more than 800 articles; after an initial screening and removal of duplicate works, the search was further refined, resulting in approximately 300 articles that were scrutinized and comprise this review. The articles were organized to describe extraction and isolation, analytical methods, pharmaceutical development, and biological and pharmacological activities [divided into nonclinical (*in vitro*, *in vivo*) and clinical studies], pharmacokinetic studies, and stability studies.

Abbreviations

6-OHDA: 6-hydroxydopamine
CCL11: C-C motif chemokine 11

CC: column chromatography
DAD: diode array detector
DPPH: 2,2-diphenyl-1-picrylhydrazyl
ELISA: enzyme-linked immunosorbent assay
ESIMS: electrospray ionization mass spectrometry
HPLC: high performance liquid chromatography
(HP)TLC: (high-performance) thin-layer chromatography
IDO: indoleamine 2,3-dioxygenase
IKK- β : I κ B kinase β
LC: liquid chromatography
LPS: lipopolysaccharide
MPLC: medium performance liquid chromatography
MS: mass spectrometry
NF- κ B: nuclear factor-kappa B
NMR: nuclear magnetic resonance
PDA: photo diode array
PK: pharmacokinetic
PLE: pressurized liquid extraction
RA: rosmarinic acid
SCORAD: severity scoring of atopic dermatitis
SFE: supercritical fluid extraction
t-BOOH: tert-butylhydroperoxide
TEWL: transepidermal water loss
TNF- α : tumor necrosis factor- α
UAE: ultrasonic-assisted extraction
UPLC: ultra performance liquid chromatography
UV-Vis: ultraviolet-visible spectroscopy

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Bibliography

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Correspondence

Maique W. Biavatti
Laboratório de Farmacognosia
Cif/CCS/UFSC
Campus Universitário/Trindade
88040-900 Florianópolis, SC
Brazil
Phone: + 55 48 37 21 34 93
maique.biavatti@ufsc.br

Introduction

The natural compound RA [(R)-(+)-rosmarinic acid, ● **Fig. 1** is a common ester derived from caffeic acid and (R)-(+)-3-(3,4-dihydroxyphenyl)lactic acid that can accumulate in high amounts in many plant species. RA is abundant in several medicinal plants of the Lamiaceae family, such as

rosemary (*Rosmarinus officinalis* L.), spearmint (*Mentha* spp.), and lemon balm (*Melissa officinalis* L.), and also in plants used in traditional Chinese medicine, such as *Perilla frutescens* (L.) Britton, *Salvia miltiorrhiza* Bunge, and *Rabdosia rubescens* (Hemsl.) H. Hara. Many studies have reported the role of RA in the biological activity of these plants as well as its pharmaceutical and biotechnological

Fig. 1 (R)-(+)-rosmarinic acid.

applications. Concerning its aspects in the biotechnology field, many reviews have been published in the last decade [1–6]. The present review covers predominantly analytical, pharmaceutical, and biological aspects of RA, including clinical trials.

Extraction, Isolation, and Analytical Methods

Several extraction protocols [7–11], separation [12–14], and chromatographic methods have been developed to optimize the extraction and identification of RA [7,12,15]. The type of solvents, temperature, extraction time, particle size of the material to be extracted, and ratio of the solvents are some of the parameters studied [16–19]. Sometimes solvent modifiers were used, such as acids, bases, and salts, and ionic solvents have also been explored [8,20,21]. Moreover, various methods and techniques used to extract polyphenols from plant materials have ended up obtaining RA as one of the principal components [22–26]. **Table 1** shows a summary of selected techniques for RA extraction. Versatile extraction of RA requires a good choice of protic solvents, temperature, and sufficient time to avoid degradation in analytical studies or optimization processes. Response surface methodology has also been used to optimize the isolation of RA [27–31]. Along with conventional extraction methods, for instance hydrodistillation, decoction, and maceration, other methods, such as PLE [32], UAE [29,33,34], SFE [35], microwave-assisted extraction [23,36–39], accelerated solvent extraction [40], and enzyme-assisted extraction [41,42], have also been employed to extract polyphenols, of which RA was identified as one of the major compounds. Nanofiltration [43–45] and solid-phase extraction [46,47] are examples of techniques used to improve the amount of RA extracted from plant materials.

Interestingly, in a study that used infusion, decoction, microwave, and ultrasonic methods to optimize the extraction of phenolic compounds from *Plectranthus* spp., the highest amount of RA was found in the decoction extract of *Plectranthus ecklonii* Benth. (Lamiaceae) (293 μ M) [48]. Cabana and collaborators [49] prepared hydrolate, decoction, and ethanolic extracts from *Satureja parvifolia* (Phil.) Epling (Lamiaceae) and demonstrated that the hydrolate extract presented the highest amount of RA.

In some studies, conventional soxhlet extraction was compared with other methods. *Dracocephalum moldavica* L. (Lamiaceae) was extracted using a soxhlet apparatus with several solvents, of which *n*-butanol extract presented the highest RA content (114.54 $\pm$ 24.70 mg/g dry extract) [50]. Soxhlet extraction was compared with the maceration method on unripe, half ripe, and full ripe *Cuminum cyminum* L. (Apiaceae) seeds [51], demonstrating that the maceration method produced a higher RA content than the soxhlet extraction. By contrast, a comparison between soxhlet and SFE of *Satureja hortensis* L. showed that soxhlet extraction with ethanol provided the highest RA content [52].

With SFE of *R. officinalis* (rosemary), comparison of CO₂ with dimethyl ether demonstrated that dimethyl ether provided the

highest RA yield [53]. The same plant leaves treated with supercritical fluid-CO₂ at 5000 psi and 40, 60, and 80 °C showed that extraction at 60 °C furnished the highest amount of RA [54]. However, comparative studies on rosemary leaves using SFE, the hydrodistillation method, and solvent extraction with different solvents showed that the RA content was highest in the solvent extraction with ethanol [55]. Again in rosemary leaves, PLE using water and ethanol as solvents, compared to SFE using neat CO₂ and supercritical CO₂ modified with ethanol, showed that PLE using ethanol at temperature (150 °C) produced the highest RA yield [56].

From these comparative studies, it cannot be concluded that there is an ideal solvent or method to obtain RA, as it depends on the combination of chosen parameters.

To provide one-step isolation and purification of RA from *S. miltiorrhiza*, an online adsorption chromatography-countercurrent chromatography was carried out after UAE, adsorbing the plant extract on the resin and immediately submitting it to high-speed countercurrent chromatography (HSCCC), which led to the isolation of RA with a purity of about 88% [12].

A template-assisted process using the supramolecular technique has also been used to extract RA from *P. frutescens* leaves. A *P. frutescens* extract, separated by supramolecular formation using flavocommelin and magnesium acetate aqueous solution followed by solvent extraction (ethyl acetate and water), yielded RA with 62.9 $\pm$ 4.5% purity [58].

Analytical techniques used to determine RA include capillary electrophoresis [59], electromechanical [60], spectroscopic [61–64], and chromatographic methods [65–71].

Some unusual electrochemical techniques have been developed, such as that reported by Franzoi et al. [72], which uses a biosensor based on laccase from the fungus *Aspergillus oryzae* and the ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophosphate (BMIPF₆) to determine RA in *M. officinalis* by square wave voltammetry. Additionally, a synthetic heterodinuclear Fe(III)/Zn(II) complex, a biomimetic complex of purple acid phosphatases, has also shown to be effective in determining RA in plant extracts [60]. The amount of RA determined by these techniques was in accordance with capillary electrophoresis data. Another electrochemical technique using dual-channel coulometric detection coupled with liquid chromatography has also been used to quantify RA in *Prunella vulgaris* L. (Lamiaceae), animal feed, and pig plasma, with minimum prepreparation steps, offering good selectivity and sensitivity [69].

Standard chromatographic techniques are the most frequent form of analysis used in the determination of RA. These can be grouped into TLC densitometry or HPTLC, and LC methods. TLC/HPTLC methods are the most accessible ones, but provide variable quantitative results since some methods possess methodological weakness. For example, integrated in the development process of a new method, a validation step is mandatory to demonstrate its reliability and the suitability. These methods used diverse stationary phases, such as normal silica gel [65,73–77] and chemically modified silica gel with amino, cyano, or octadecyl groups [70,78,79]. Using densitometry, Janicsak et al. [76] showed the RA content in some species of Lamiaceae ranging from 0.01 to 9.30 mg/g.

Regarding LC methods, they have been most widely used for the separation, detection, and quantification of RA in plant extracts, providing a wide range of concentrations of RA in several Lamiaceae species. UV-Vis or DAD/PDA are the most widely used detectors [66,67,68,75,80], followed by an MS detector [67,71,75,81].

Table 1 Summary of extraction and isolation studies for rosmarinic acid.

Plant studied (Family), location, (ref)	Extraction method	Quantity crude material	Extraction solvents	Temperature (°C)	Time of extraction	Concentration of RA in the crude extract (mg/g)	Method of separation/ quantification
<i>Orthosiphon stamineus</i> leaves, (Lamiaceae) Malaysia [209]	Maceration	10 g	H ₂ O	40	2 h	5.40	HPLC equipped with a Li-Chrosorb RP-18 column (250 × 4.6 mm, 5 μm) and H ₂ O-MeOH-THF (45:50:5) as the mobile phase
					4 h	6.61	
					8 h	6.71	
			MeOH		2 h	5.41	
					4 h	6.48	
					8 h	7.99	
			H ₂ O-MeOH 1:1		2 h	9.03	
					4 h	9.78	
					8 h	9.54	
			(CH ₃) ₂ CO-H ₂ O (3:7)		2 h	7.35	
4 h	7.43						
8 h	7.72						
<i>Orthosiphon stamineus</i> leaves, (Lamiaceae) Germany [210]	Maceration	100 g	EtOH-H ₂ O (1:1)	Room temperature	5 days	0.45	HPLC equipped with a guard column and LiChrosphere RP-18 column (125 × 4 mm, 5 μm). Eluent: gradient of H ₃ CCN-H ₃ PO ₄ (99.9:0.1)/ H ₂ O-H ₃ PO ₄ (98:2)
			EtOH-H ₂ O (3:7)		0.58		
<i>Salvia officinalis</i> leaves, (Lamiaceae) USA [15]	Maceration	30 kg	EtOH-H ₂ O (95:5)	Room temperature	2 weeks	0.02	Liquid-liquid extraction water-(Hex, EtOAc, n-BuOH), CC on silica gel CHCl ₃ -MeOH gradient condition, Sephadex LH-20 column eluted with MeOH, Li-chroprep RP-18 column using MeOH-H ₂ O (3:7), and EtOAc-MeOH-H ₂ O (12:1:1)
<i>Salvia officinalis</i> leaves, (Lamiaceae) Brazil [67]	Maceration	10 g	Aqueous ethanol	80		45–55	Extraction with (Et) ₂ O fractionation with Chromatron (centrifugal thin-layer chromatograph) eluted with EtOAc-hexane-AcOH (3:6:1)
<i>Rosmarinus officinalis</i> leaves, (Lamiaceae) Spain [56]	Pressurized liquid extraction	1 g	EtOH	50	20 min	12.37 ± 0.38	UPLC-ESIMS Hypersil Gold column (50 × 2.1 mm) using a gradient of CH ₃ CN-H ₂ O (0.1 % formic acid).
				100		16.00 ± 0.98	
				150		16.78 ± 0.64	
				200		9.12 ± 0.34	
			H ₂ O	50		9.81 ± 0.89	
				100		14.19 ± 0.85	
				150		9.85 ± 0.38	
				200		8.60 ± 1.16	
<i>Cordia americana</i> leaves, (Boraginaceae) Brazil [211]	Extraction assisted by heating	1140.94 g	EtOH	Soxhlet		0.011	CC on Sephadex LH-20 and MeOH used as the eluent, successive flash chromatography over an RP-18 eluted with a gradient of MeOH-H ₂ O
						84.4	HPLC, LiChrosphere RP-18 column (5 × 100 mm; 5 μm), CH ₃ CN-H ₂ O gradient (0.1 % formic acid)
<i>Thunbergia laurifolia</i> leaves, (Acanthaceae) Thailand [212]	Maceration	20 g	EtOH-H ₂ O (95:5)	Room temperature	3 times 72 h		HPLC equipped with a 4.6 × 250 mm Cosmosil 5C18-AR-II column, isocratic elution with H ₂ O-MeOH-AcOH (65:35:0.1)
Nakhon Pathom						38.80	
Nonthaburi						1.56	
Prakan							
Nakhon Sawan						14.86	
Prachin Buri						53.50	
Phetchabun						0.87	
Samut Prakan	3.01						

continue

continued

Table 1 Continued

Plant studied (Family), location, (ref)	Extraction method	Quantity crude material	Extraction solvents	Temperature (°C)	Time of extraction	Concentration of RA in the crude extract (mg/g)	Method of separation/quantification
<i>Mentha piperita</i> leaves, (Lamiaceae) Iraq [16]	Maceration assisted by ultrasound	1 g	EtOH-H ₂ O (4:1)	40	1 h	1.43	HPLC instrument, C18 column (4.6 × 250 mm, 5 mm), isocratic MeOH-H ₂ O + 0.1 % AcOH (4:1)
<i>Mentha longifolia</i> leaves, (Lamiaceae) Iraq						2.08	
<i>Osimum basilicum</i> leaves, (Lamiaceae) Iraq						3.06	
<i>Maranta depressa</i> leaves, (Marantaceae) Germany [213]	Extraction assisted by sonication	50 mg	EtOH 70%	70	10 min	12.6	HPLC on a Hypersil ODS column (5 mm, 280 mm × 40 mm) and 45 % MeOH/0.01 % H ₃ PO ₄ used as the eluent
<i>Maranta leuconeura</i> "Fascinator" leaves, (Marantaceae) Germany						8.7	
<i>Maranta leuconeura</i> var. <i>kerchoviana</i> leaves, (Marantaceae) Germany						8.1	
<i>Maranta leuconeura</i> var. <i>mas-sangeana</i> leaves, (Marantaceae) Germany						7.8	
<i>Canna edulis</i> leaves, (Cannaceae) Germany						37.2	
<i>Canna indica</i> leaves, (Cannaceae) Germany						50.7	
<i>Perilla frutescens</i> leaves, (Lamiaceae) Japan [18]	Maceration	650 g	MeOH	Room temperature		1.9	Acidification, amberlite column eluted with acidified H ₂ O and MeOH, droplet countercurrent chromatography eluted with CHCl ₃ - <i>n</i> -BuOH-MeOH-H ₂ O (9:2:12:8) and CC (Diaion HP20AG) eluted with H ₂ O-MeOH in gradient conditions
<i>Melissa officinalis</i> leaves, (Lamiaceae) Slovak [19]	Maceration		<i>i</i> PrOH-H ₂ O (39:61)	66	1 h	72.6 ± 3.1	HPLC analysis RP18, 250 × 4 mm, 5 µm, gradient condition of CH ₃ CN-H ₂ O, 0.1 % CF ₃ CO ₂ H
<i>Anthurium versicolor</i> leaves, (Araceae) Ecuador [214]	Maceration	195 g	MeOH	Room temperature		0.031	Chromatography on Sephadex LH-20, RP-HPLC on a C18 Bondapack column (30 cm × 7.8 mm) eluent isocratic MeOH-H ₂ O (1:1)
<i>Tournefortia sarmentosa</i> (Boraginaceae) Taiwan [215]	Maceration	20 kg	EtOH-H ₂ O (85:15)	50		0.625	Diaion HP-20 column chromatography using a gradient of MeOH-H ₂ O and Sephadex LH-20 using MeOH 80 %
<i>Salvia officinalis</i> (Lamiaceae) New Zealand [216]	Maceration	50 g	Me ₂ CO-H ₂ O (7:3)	Room temperature		48.65	Diaion HP-20 column, eluent H ₂ O then MeOH, Sephadex LH-20 column MeOH-H ₂ O (7:3), HPLC equipped with an RP-18 column elution gradient of CH ₃ CN-H ₂ O (2 % AcOH)

continued

Table 1 Continued

Plant studied (Family), location, (ref)	Extraction method	Quantity crude material	Extraction solvents	Temperature (°C)	Time of extraction	Concentration of RA in the crude extract (mg/g)	Method of separation/quantification
<i>Sanicula europaea</i> aerial parts, (Apiaceae) Turkey [217]	Maceration	940 g	EtOH-H ₂ O (1:1)	65	1 h	0.26	Column chromatography on silica gel 60 G mixed with silica gel 60 HF 254 and elution performed with CHCl ₃ -MeOH-H ₂ O (61:32:7)
<i>Perilla frutescens</i> seeds, (Lamiaceae) Japan [218]	Extraction assisted by heating	800 g	EtOH	Reflux	2 h	0.024	Liquid-liquid extraction Hex, EtOAc-H ₂ O, EtOAc. Fraction purified by CC silica gel, Sephadex LH-20 and HPLC equipped with an ODS column, MeOH-H ₂ O (1:1) used as the eluent
<i>Nepeta cadmea</i> aerial parts, (Lamiaceae) Turkey [14]	Maceration	1.25 kg	MeOH	Room temperature	30 days	0.024	Liquid-liquid extraction Hex-MeOH, H ₂ O-(EtOAc, <i>n</i> -BuOH). <i>n</i> -BuOH fraction purified with CC on Dianion HP-20 MeOH-H ₂ O Gradient. CC on silica gel eluted with CHCl ₃ -MeOH and HPLC equipped with a C-18 column eluted with a gradient of MeOH-H ₂ O
<i>Pulsatilla koreana</i> roots, (Ranunculaceae) South Korea [219]	Maceration	1.2 kg	MeOH and CH ₂ Cl ₂	Room temperature		0.017	Vacuum flash chromatography on RP-18 using MeOH and H ₂ O as the eluent in gradient condition. Further purification took place with reversed-phase HPLC (YM-C-ODS column; H ₂ O-MeOH gradient)
<i>Hyssopus cuspidatus</i> whole plant, (Lamiaceae) China [220]	Maceration assisted by ultrasonication	1.5 kg	EtOH	20–30	30 min	0.01	Diaion HP-20 resin column eluted with a gradient of MeOH-H ₂ O acetone, silica gel CC eluted with CHCl ₃ -MeOH-H ₂ O reversed-phase HPLC with mobile phase MeOH-H ₂ O (2:6) and reversed-phase HPLC CH ₃ CN-H ₂ O (1:9) as the mobile phase
<i>Baccharis chilco</i> aerial parts, (Asteraceae) Colombia [10]	Extraction assisted by heating	446 g	CH ₂ Cl ₂ and EtOH	Reflux	2 h	0.045	CC on silica gel with CH ₂ Cl ₂ -EtOH used as the eluent. H ₂ O (alkaline)-EtOAc separation and HPLC purification of the organic phase using isocratic the condition of MeOH-H ₂ O (2:3)
<i>Helicteres isora</i> fruits, (Sterculiaceae) Indonesia [221]	Extraction assisted by heating	4 kg	MeOH	Reflux 60	7 h	0.078	Liquid-liquid extraction CHCl ₃ -MeOH-H ₂ O (5:3:8) and then with EtOAc and <i>n</i> -BuOH. CC on Sephadex LH-20 using MeOH-H ₂ O (2:1) as the eluent. A second purification on Sephadex LH-20 eluted with MeOH-H ₂ O (2:1), followed by successive purification on an MPLC silica gel column and an RP-18 column eluted with EtOAc-MeOH-H ₂ O (60:25:15) and H ₂ O-MeOH (3:1), respectively

continued

Table 1 Continued

Plant studied (Family), location, (ref)	Extraction method	Quantity crude material	Extraction solvents	Temperature (°C)	Time of extraction	Concentration of RA in the crude extract (mg/g)	Method of separation/quantification
<i>Hedyotis scandens</i> (Rubiaceae) [222]	Percolation	9 kg	EtOH 95%	Room temperature		0.006	Liquid-liquid extraction H ₂ O, petroleum ether, EtOAc, and <i>n</i> -BuOH. CC on silica gel eluted with a gradient of CHCl ₃ -MeOH. Further CC on silica gel eluted with a gradient of CHCl ₃ -MeOH
<i>Melissa officinalis</i> leaves, (Lamiaceae) [223]	Extraction assisted by stirring	100 g	Acidified H ₂ O	80–100	45 min	13	Liquid-liquid extraction with Et ₂ O, Sephadex LH-20 using MeOH-H ₂ O (7:3). Recrystallization at 4 °C
<i>Zostera noltii</i> leaves, (Zosteraceae) France [224]	Extraction assisted by heating	500 g	MeOH	Reflux		14.4	Liquid-liquid extraction CHCl ₃ , EtOAc and H ₂ O, then flash chromatography on a silica gel using EtOAc-MeOH (95:5) as the eluent
Collection July						8.10 ± 0.11	HPLC equipped with a Hypersil GOLD C8 column (5 µm particle size, 250 × 4.6 mm) and MeOH-H ₂ O (0.1 %TFA) used as the eluent in gradient conditions
Collection December						2.17 ± 0.27	
Collection January						8.65 ± 0.11	

The majority of the developed methods use UV-Vis or DAD/PDA detectors for the determination of RA in plants and extracts, while an MS detector is preferable for determination of RA in formulations and pharmacokinetic studies. Bandoniene et al. [80] used single ion monitoring mode at m/z 383 $[M + Na]^+$ to quantify RA in several *Salvia* spp. and *Borago officinalis* L. (Boraginaceae), while Berhow et al. [75] used m/z 359, corresponding to the $[M - H]^-$ mass ion of RA, to quantify RA in *Ocimum canum* Sims (Lamiaceae). Moreover, LC/tandem mass spectrometry has also been exploited to determine RA and some other components in beagle dog plasma [82] during pharmacokinetic studies. Here, the deprotonated molecule $[M - H]^-$ was also used, since the sensitivity in the negative mode was higher than that in the positive mode. The limit of detection was found to be 1.0 ng/mL. Meanwhile, an HPLC-DAD-DPPH method has been used for online detection of the radical scavenging activity of RA [80]. After HPLC separation and UV detection at 280 nm, the analytes reacted post-column with the DPPH at a concentration of 50 mg/mL in methanol. Trute and Nahrstedt [83] developed a laborious two-step derivatization gas chromatography method to analyze RA enantiomers. Regarding spectroscopic methods, a spectrophotometric analysis developed by Oztürk et al. [61], based on the complexation of RA with zirconium ions, was used for the quantification of RA in 11 *Salvia* species. Infrared spectroscopy has also been used to quantify RA in the Lamiaceae family [62,64]. While Stehfest et al. [64] used the first derivative of the spectral region for quantification purposes, Saltas et al. [62] used the second derivative of the spectral region 1344–806 cm^{-1} .

NMR spectroscopy has also been used to identify and quantify RA in methanol and ethanol extracts of plant species of the Lamiaceae family [63,84], based on variable-temperature two-dimensional 1H - 1H double quantum filter correlation spectroscopy (DQF-COSY), 1H - ^{13}C heteronuclear multiple-quantum coherence

(HMQC), and 1H - ^{13}C heteronuclear multiple-bond correlation (HMBC) gradient NMR spectroscopy.

Pharmacological and Biological Activities

The pharmacological and biological activities of RA and RA-containing plant extracts have received considerable attention. Many scientific reports and patents have explored these properties, ranging in complexity from *in vitro* to clinical studies.

The exceptional antioxidant activity of RA, in parallel with the effects on cell signalling pathways and gene expression, contributes to the majority of the biological properties and technological applications covered by this review [28,85–91]. As a result, RA antioxidant and pro-oxidant profiles [92,93] have been comprehensively studied, through multiple assays [93–101]. The four phenolic hydrogens underwrite its ability to modulate free radical scavenging, in combination with two catechol moieties that provide the suitable polarity for RA to penetrate the lipid bilayers and protect them against oxidation without disturbing their structure [94,96]. Electrochemical investigations have revealed that the first oxidation step is associated with the caffeic acid moiety, whereas the second oxidation step corresponds to the oxidation of the 3,4-dihydroxyphenyl lactic acid residue [94]. Due to the combination of these structural features, the antioxidant potential of RA is higher than that of the other hydroxycinnamic acid derivatives [96,102–104].

Besides the antioxidant potential, RA has been reported to present a multitude of pharmacological and biological activities. An in-depth description of each would be beyond the scope of this review, but a compilation and analysis of these reports is presented below (studies reporting solely extracts results were not

included, unless otherwise stated). It is divided into three sections: *in vitro*, *in vivo*, and clinical studies.

In vitro studies

RA exhibits a wide collection of biological activities *in vitro*, including antioxidant, anti-inflammatory, antimutagenic, antigenotoxic, cytotoxic, antimetastatic, antiangiogenic, neuroprotective, antimicrobial, immunomodulatory, melanogenic, and antivenom effects. The array of active concentrations reported in the studies covers different magnitudes, which raises concerns about specificity. Additionally, active concentrations in the millimolar, or even high micromolar range, are unlikely to translate into clinical effects due to limitations related to plasma levels and biodistribution in humans (see section “Pharmacokinetics in Humans”). ● **Table 2** provides a non-exhaustive list of *in vitro* findings obtained with RA.

Studies that focus on the technological application of RA have reported that this phenolic acid is a good bioprotective agent against fungal infections in crops [105], and a good candidate for partial monolignol substitution via bioengineering approaches, aiming at more efficient utilization of plant fibers for biofuels or livestock production [106].

Pharmacokinetic studies of RA using *in vitro* models have also been conducted by some research groups. Qiang et al. compared the permeability and phase II biotransformation of RA as a pure compound and also in herbal extracts using human intestinal epithelial Caco-2 cell monolayers. The apparent permeability coefficient (P_{app}) obtained for RA was 0.2×10^{-6} cm/s, indicating a low permeability profile [107]. In agreement, Konishi and Kobayashi reported that *in vitro* intestinal absorption of RA was rather low. The majority of RA loaded on the apical side of Caco-2 cells was not transported, and the permeation occurred mainly via paracellular diffusion [108]. Moreover, RA appeared to be unsusceptible to chemical and enzymatic hydrolysis in Caco-2 cells and gastrointestinal models [108,109]. Conversely, the addition of *Lactobacillus johnsonii* cells to the rosemary extract resulted in a substantial hydrolysis of RA [109]. Taken together, these results suggest that RA is further metabolized and degraded by gut microflora, in accordance with *in vivo* studies (see “Pharmacokinetics in Animals” section). RA metabolites are then efficiently absorbed and distributed by the monocarboxylic acid transporter within the body [108]. Qiang et al. demonstrated that RA permeability significantly increased after treatment with β -glucuronidase/sulfatase [107], and Falé et al. demonstrated that the presence of benzoic acid, a substrate of monocarboxylic acid transporter, or flavonoids (i.e., luteolin and apigenin) can decrease RA permeation [110], supporting the involvement of membrane transporters in the uptake of RA.

The interaction of RA with other pharmaceutical relevant transporters and enzymes has been studied *in vitro*. Lin et al. reported RA inhibits UDP-glucuronosyltransferase activity [111], and Li et al. showed that RA could decrease the transcription and expression of P-glycoprotein, promoting the reversal of multidrug resistance phenomena [112].

In vivo studies

By compiling the *in vivo* studies, it was found that numerous biological studies corroborate the *in vitro* hypothesis. A significant prevalence of anti-inflammatory, antitumoral, and tissue damage prevention studies was also found. These reports highlight, once again, antioxidant and radical scavenging activities as key factors in the *in vivo* outcomes reported for RA.

The search for antitumoral compounds also included investigations of RA against different types of cancer [113–117]. Karmokar et al. showed that chronic consumption of RA (0.3% w/w chow supplementation) for 8 weeks inhibited colon carcinogenesis in mice, and produced quantifiable levels of the parent compound in the plasma and the intestinal tract [118]. Additionally, RA suppressed retinal neovascularization [119], and exhibited transcorneal penetration when the RA-containing polyherbal formulation was instilled into rabbit eyes [120].

No increase was found in the frequency of micronuclei in mice treated orally with 50–200 mg/kg of RA, indicating that RA does not affect chromosomal integrity [121]. In fact, RA showed antimutagenic effects, protecting animals against doxorubicin [121], ethanol [122], and γ ray-induced DNA damage [123], assessed by the comet and micronucleus assays using murine models.

Studies exploring the anti-inflammatory activity of RA are also frequent [124–127]. Youn et al. showed that RA (daily intraperitoneal injections, 50 mg/kg) suppressed synovitis in a murine collagen induced arthritis model [128], while other groups reported the inhibition of allergic inflammatory reactions [129] and airway inflammation [130,131] as well as atopic dermatitis [132,133]. Jiang et al. reported that RA, administered intravenously (25 and 50 mg/kg), either alone or in combination with imipenem, protected rats against experimental sepsis by decreasing local and systemic levels of an extensive spectrum of inflammatory mediators [134]. Additionally, oral administration of RA (2 mg/body for 3 days) inhibited diesel exhaust particle-induced lung injury in mice by reducing the expression of proinflammatory molecules and antioxidative activities [135].

In regard to anti-infective potential, RA presented *in vivo* antiviral activity against the Japanese encephalitis virus, a member of the Flaviviruses family [136]. At 8 to 9 days postinfection, the mortality of mice treated intraperitoneally twice daily (25 mg/kg) was reduced in comparison to untreated animals. This effect was mediated by decreased viral loads, and also by reduced levels of proinflammatory cytokines [136].

RA was also shown to be immunosuppressant, improving skin [137] and islet allograft survivals in murine models [138]. Anti-hemorrhagic, antithrombotic, and antiplatelet effects, along with the direct neutralization of multiple snake venoms and fish toxins, have also been reported for RA or RA-containing extracts [139–147], corroborating for a potentially beneficial role of RA for the treatment of poisoning accidents, already described in the *in vitro* section (● **Table 2**).

Protective effects of RA in tissue or organs have been demonstrated. Domitrovic et al. showed that oral treatment with RA (1–5 mg/kg) for two consecutive days improved cisplatin-induced kidney injury in mice by inhibiting oxidative stress, inflammation (TNF- α and NF- κ B), and apoptosis [148]. Other groups reported similar profiles [149–152], i.e., inhibition of diabetes-related renal damage [153] or inhibition of gentamicin sulphate-induced renal oxidative damage in rats treated orally with 50 mg/kg for 12 days [154,155]. Also, memory protective effects of RA in an Alzheimer's model (β -amyloid neurotoxicity) was attributed to the radical scavenging potential of the molecule [156]. Cardio-protection [157,158], inhibition of endothelial tissue damage [159], and reduction of multiple organ failure in thermal injury [160] were linked to the antioxidant and anti-inflammatory effects of RA *in vivo*. Liver protection effects against cholestatic fibrosis, ischemia-reperfusion injury, CCl₄, and lipopolysaccharide-induced damage were also reported at oral doses ranging from 2.5 to 50 mg/kg [160–165].

Table 2 Summary of *in vitro* studies with isolated rosmarinic acid.

First author, year (ref)	Method	Concentration	Main findings
Anti-inflammatory			
Lembo et al., 2014, 2011 [225, 226]	Cell viability (HaCaT cells) Cytokine modulation by qRT-PCR	2.7–55 μ M	prevention of UVB-induced inflammation
Ku et al., 2013 [124]	ELISA (primary human umbilical vein endothelial cells)	0.1–2 μ M	inhibition of endothelial protein C receptor shedding
Moon et al., 2010 [227]	Cell viability (U937 human leukemia cells)	15–60 μ M	↓ TNF- α -induced ROS generation ↓ NF- κ B activation ↑ TNF- α -induced apoptosis
Huang et al., 2009 [228]	LPS stimulation (RAW 264.7 mouse macrophage cells)	2.67 μ M	↓ LPS-induced prostaglandin E2 and nitric oxide production
Zdarilová et al., 2009 [229]	LPS stimulation (primary cultured human gingival fibroblasts)	1 μ g/mL	↓ oxidative damage ↓ inflammation
Kim et al., 2008 [230]	LPS inflammatory stimulation (BMDCs bone marrow-derived dendritic cells)	0.1–200 μ M	↓ cell maturation and migration ↓ monocyte chemoattractant protein-1 ↓ macrophage inflammatory protein-1 α
Scheckel et al., 2008 [231]	Luciferase assay (HT-29 colon cancer and MCF10 A non-malignant epithelial cells)	5–20 μ M	↓ AP-1-dependent activation of cyclooxygenase-2 in human cancer and normal cells
Lee et al., 2006 [232]	ELISA and Western blotting (human dermal fibroblast cells)	1–40 μ M IC ₅₀ = 9.1–15.8 μ M	↓ expression of CCL11 and C-C motif chemokine 11 receptor (CCR3) ↓ IKK- β activity
Antiproliferative and Antimutagenic			
Zhang et al., 2011 [233]	Cell viability (HSC-T6 hepatic stellate cells)	1–16 μ g/mL IC ₅₀ = 7.1 μ g/mL	↓ cell proliferation ↑ apoptosis
Xu et al., 2010 [113]	Wound healing, adhesion and Transwell assays (Ls174-T human colon carcinoma cells)	5–300 μ g/mL IC ₅₀ < 20 μ g/mL	antimetastasis effect
Xu et al., 2010 [234]	Cell viability (MDA-MB-231BO human bone-homing breast cancer cells) and wound healing assays	1–300 μ g/mL	↓ tumoral cells migration (IC ₅₀ = 118 μ g/mL) bone protection <i>in vitro</i>
Kim et al., 2009 [119]	Cell viability and morphological changes (HRMEC human retina microvascular endothelial cells)	10–100 μ M	antiangiogenic activity ↓ cell proliferation ↓ tube formation
Xavier et al., 2008, 2009 [235, 236]	Cell viability (HCT15 and CO115 human colorectal carcinoma-derived cells)	10–100 μ M	↓ cell proliferation ↑ apoptosis
Hur et al., 2004, 2007 [237, 238]	Flow cytometry (peripheral blood mononuclear cells obtained from rheumatoid arthritis patients and Jurkat acute T cell leukemia cells)	3–100 μ M	↓ cell proliferation ↑ apoptosis
Huang et al., 2006 [239]	Cell viability and migration assays (HUVEC human umbilical vein endothelial cells)	12.5–200 μ M	↓ several steps of angiogenesis
Kolettas et al., 2006 [240]	Cell viability (Jurkat human T lymphoma cells)	10–150 μ M	↓ cell proliferation ↑ apoptosis
Vattem et al., 2006 [241]	AMES and supercoiled DNA strand scission assay	500 μ g/plate	antimutagenic effect
Yoshida et al., 2005 [242]	Cell viability (MK-1, HeLa, and B16F10 cells)	MK-1, GI ₅₀ = 119 μ M HeLa, GI ₅₀ = 75 μ M B16F10, GI ₅₀ = 16 μ M	↓ cell proliferation
Cytoprotection			
Alcaraz et al., 2014 [243]	Micronucleus (human lymphocytes) Cell viability (PNT2 and B16F10 cells)	10–40 μ M	radioprotection in normal cells ↑ radio-induced damage in melanoma cells
Braidly et al., 2014 [244]	Cell viability (primary cultured human neurons)	0.01–1 mg/mL	protection against ciguatera-induced neurotoxicity
Costa et al., 2013 [245]	Cell viability (A172 human astrocyte cells)	30 μ g/mL	protection against H ₂ O ₂ -induced oxidative damage
Jeon et al., 2013 [246]	Cell viability (primary cultured rat hepatocytes)	1–100 μ M	cytoprotection against hypoxia-induced injury
Kim et al., 2013 [247]; Jeong et al., 2011 [248]	Cell viability (HEI-OC1 auditory cell line) Fluorescence microscopy (Rat Corti primary explants)	1–100 μ M	protection against Cd ²⁺ -induced or cisplatin-induced ototoxicity protection against cisplatin-induced destruction of hair cell arrays <i>ex vivo</i>
Yang et al., 2013 [249]	Cell viability (HepG2 human hepatoma cells)	10–26.84 μ g/mL	protection against t-BOOH-induced cytotoxicity
Du et al., 2010 [250]; Ren et al., 2009 [251]	Cell viability (MES23.5 dopaminergic cells)	0.001–100 μ M	protection against 1-methyl-4-phenylpyridinium (MPP ⁺) and 6-OHDA-induced neurotoxicity
Furtado et al., 2010 [252]	Micronucleus and comet assay (V79 cells)	0.28–1.12 mM	protection against doxorubicin-induced genotoxicity
Fallarini et al., 2009 [253]	Cell viability [differentiated SH-SY5Y and SK-N-BE(2) human neuroblastoma cells]	10–100 μ M EC ₅₀ = 0.9–3.7 μ M	protection against t-BOOH-induced oxidative stress ↓ excitotoxicity ↓ ischaemia-reperfusion-induced neuronal death
Lee et al., 2008 [254]	Cell viability (SH-SY5Y human dopaminergic neuronal cells)	14–56 μ M	protection against H ₂ O ₂ -induced neurotoxicity ↓ apoptosis

continued

Table 2 Continued

First author, year (ref)	Method	Concentration	Main findings
Salimei et al., 2007 [255]	Cytofluorimetric approach (K562, NPA and ARO cells)	25 μ M	↓ sorbitol-induced apoptosis
Iuvone et al., 2006 [256]	Cell viability (PC12 adrenal medulla cells)	0.0036–36 μ g/mL	↓ β -amyloid-induced cell death
Psotova et al., 2006 [257]	Cell viability (HaCaT human keratinocyte cells)	0.9–18 μ g/mL	photoprotection against UVA-induced damage
Yan et al., 2006 [258]	Cell viability (PC12 cells)	100 μ M	protection against glutamate-induced cell death ↓ apoptosis
Gao et al., 2005 [259]	Cell viability (primary cultured rat astrocytes)	10–40 μ M	protection against H ₂ O ₂ -induced cell death ↓ apoptosis
Kim et al., 2005 [260]	Cell viability (H9c2 cardiomyoblast cells)	1–20 μ g/mL	protection against adriamycin-induced apoptosis ↓ apoptosis
Chlopcikova et al., 2004 [261]	Cell viability (primary cultured rat cardiomyocytes)	100–200 μ M	protection against doxorubicin-induced cell death ↓ lipid peroxidation (IC ₅₀ = 8.17 μ M)
Renzulli et al., 2004 [262]	Cell viability (Hep G2 human hepatoma-derived cells)	2.5–100 μ M	protection against aflatoxin B1 and ochratoxin A-induced cytotoxicity
Immunomodulation			
Lee et al., 2007 [263]	IFN- γ stimulation (BMDCs murine bone marrow-derived dendritic cells)	1–100 μ M	↓ IDO-dependent T cell suppression ↓ functional expression of IDO
Ahn et al., 2003 [264]; Kang et al., 2003 [265]; Won et al., 2003 [266]; Yun et al., 2003 [137]	Binding assay Cell proliferation and differentiation	0.1–1000 μ M IC ₅₀ = 5.6–14 μ M	inhibition of lymphocyte cell-specific kinase Src-homology 2 domain binding ↓ T cell activation ↓ T cell proliferation
Kang et al., 2003 [267]	Luciferase and Ca ²⁺ mobilization assays (Jurkat T cells)	5–30 μ M	↓ Ca ²⁺ -dependent pathways of T-cell antigen receptor-mediated signalling
Sahu et al., 1999 [268]; Peake et al., 1991 [269]	Binding assays C3 and C5 convertase assays	0.01–10 mM	↓ complement activation binding to activated C3b C5 convertase inhibition
Miscellaneous			
Abedini et al., 2013 [270]	Minimal inhibitory concentration/minimal bactericidal concentration by broth microdilution	0.0093–2.5 mg/mL	antimicrobial activity
Airoidi et al., 2013 [271]	NMR spectroscopy	1 mM	binding to β -amyloid oligomers (Alzheimer's disease)
Marcelo et al., 2013 [272]; Yin et al., 2008 [273]	NMR spectroscopy Molecular Modelling	333 μ M 50 mM	binding to Acetylcholinesterase (Alzheimer's disease)
Slobodníková et al., 2013 [274]	Minimal inhibitory concentration/minimal bactericidal concentration by broth microdilution Biofilm regrowth technique	156–5000 μ g/mL	antimicrobial activity inactive as biofilm-eradicator
Yang et al., 2012 [161]	Cellular differentiation reversal (primary cultured hepatic stellate cells)	135–270 μ M	antifibrotic effect ↓ epigenetic peroxisomal proliferator-activated receptor γ repression reversal of activated cellular phenotypes
Dos Santos et al., 2010, 2011 [142, 143]; Ticli et al., 2005 [144]	Phospholipase ₂ enzymatic activity inhibition Molecular modelling Muscle-damaging and neuromuscular-blocking activities	13.7 μ g/mL	antivenom effects <i>in vitro</i> and <i>ex vivo</i>
Lin et al., 2011 [275]	Enzymatic activity inhibition	0.01–0.4 mM	tyrosinase and α -glucosidase inhibition
Murata et al., 2011 [276]; Ippoushi et al., 2000 [277]	Enzymatic activity inhibition	0.03–1 mM IC ₅₀ = 309 μ M	hyaluronidase inhibition
Falé et al., 2008, 2009 [278, 279]	Enzymatic activity inhibition	IC ₅₀ = 440 μ g/mL	acetylcholinesterase inhibition (Alzheimer's disease)
Lee et al., 2007 [280]	Melanin content determination (B16 melanoma cells)	1–100 μ M	↑ melanogenesis
Kang et al., 2004 [281]	Enzymatic activity inhibition	IC ₅₀ = 16.8 μ M	tyrosinase inhibition
McCue et al., 2004 [282]	Enzymatic activity inhibition	0.07–0.42 mM	amylase inhibition
Makino et al., 2000 [151]	Cell viability (primary cultured murine mesangial cells)	1–25 μ g/mL IC ₅₀ = 1.4–3.8 μ g/mL	↓ cell proliferation
Simpol et al., 1994 [283]	Histamine release inhibition (rat mast cells)	IC ₅₀ = 18 μ M	↓ histamine release

↑ Increase; ↓ decrease/inhibition; NA – not available; Most studies used multiple assays/endpoints for the pharmacological evaluation of RA; For a complete methodological assessment, please refer to the original article

The neuroprotective effect of RA was studied in animal models of central nervous system diseases. Mushtaq et al. showed that oral treatment with RA (10 mg/kg) for 21 days significantly reduced the level of lipid peroxidation in multiple areas of the brain in diabetic rats, together with modulation of cholinergic neurotransmission [166]. At doses higher than 50 mg/kg, RA produced a significant anti-inflammatory effect in rats submitted to an experimental ischemic diabetic stroke model [167]. In a Parkinson's disease model in mice, 6-OHDA-induced degeneration of the nigrostriatal dopaminergic system was reversed by 21 days of oral treatment with RA at 20 mg/kg [168]. A number of groups reported that administration of RA (orally or intraperitoneally) alleviated stress symptoms [169–173] and depressive-like behaviors [174–176], and produced anxiolytic-like effects, without exerting locomotor alterations or DNA damage in brain tissue [177]. Additionally, subchronic oral RA treatment of mice (up to 3 weeks) has a cognitive-enhancing effect [178], and, in a model of Amyotrophic lateral sclerosis, RA administered intraperitoneally (0.13 mg/kg, twice a week) significantly delayed motor dysfunction, attenuated motor neuron degeneration, and improved clinical outcomes and lifespan [179]. Finally, an unusual preclinical study in a Rhesus monkey model was conducted to determine the effect of the topical application of RA on the progression of plaque-induced gingivitis. Six young adult (4–6 years) male Rhesus monkeys (*Macaca mulatta*) randomly assigned to 3 groups of 2 each (A, B and C) received a topical application of vehicle alone, the drug ebselen (1%), and RA (5%) twice weekly for two weeks. To promote plaque retention, the chow was softened with water prior to feeding. Clinical evidence of gingivitis (erythema, edema) was apparent after 2–3 days, with established gingivitis (GI = 2) apparent in all animals after one week. Based on these preliminary studies, the authors concluded that at least in the short term, ebselen and RA are effective at reducing both gingival inflammation and plaque accumulation when topically applied [180].

Clinical studies with rosmarinic acid containing extracts

As a widespread metabolite, several traditional plants have been clinically studied using RA as a chemical marker or as an active compound. Different clinical protocols designed to assess the anti-inflammatory effects and the antioxidant potential of plants containing RA have been employed.

Initially, links between oxidative stress and adverse health effects have been suggested; for example, Ranjbar et al. [181] investigated the antioxidant influence of an *Echium amoenum* Fisch & C.A. Mey (Boraginaceae) decoction in healthy volunteers using a cross-sectional before/after clinical trial. The authors considered *E. amoenum*, one of the most important medicinal plants in Iranian traditional medicine (despite its hepatotoxic pyrrolizidine alkaloids [182]) to be a rich source of RA and flavonoids. They randomly selected thirty-eight volunteers (18–25 years old), students at Arak University of Medical Sciences, who were interviewed by a specialized physician before receiving the *E. amoenum* flower decoction (7 mg/kg) twice daily (morning and evening) for 2 weeks. The authors found a significant decrease ($p < 0.05$) in lipid peroxidation (24.65 ± 11.33 to 19.05 ± 9.7 nmol/mL), an increase in total blood antioxidant capacity ($p < 0.05$; 1.46 ± 0.51 to 1.70 ± 0.36 mmol/mL), as well as an increase ($p < 0.001$) in total thiol molecules (0.49 ± 0.11 to 0.56 ± 0.12 mmol), after administration of the decoction. In their view, this is the mechanism by which RA and antioxidants protect the human body from various diseases. This study has a ma-

ior limitation, as the authors administered a decoction that was not standardized in terms of RA content.

With a similar objective, a crossover randomized controlled trial study [183] detected, by means of LC-quadrupole time-of-flight, phenolic acids (among them RA) and aromatic compounds in human plasma 24 h after consumption of a blueberry drink containing 766 mg total polyphenols by healthy volunteers ($n = 10$). The primary outcome was the measure of flow-mediated dilation. Flow-mediated dilation increased after 1 h of consumption and then plateaued. According to the authors, increases in flow-mediated dilation were closely linked to increases in circulating phenolic metabolites and decreases in neutrophil NADPH oxidase activity at 1–2 and 6 h. The authors reported limitations when interpreting the trial datasets, such as the short time frame, causality, and the population studied.

Also focusing on antioxidant foods, a study was conducted with 11 healthy volunteers consuming two kinds of burger meat – seasoned or unseasoned with a spice blend [184]. The production of malondialdehyde in the burgers and the malondialdehyde concentration in plasma and urine after ingestion were measured, since the formation of malondialdehyde has implications for atherogenesis and carcinogenesis [185]. RA from oregano was monitored to assess the effect of cooking on the spice antioxidant content. Forty percent (19 mg) of the rosmarinic acid added remained in the spiced burger after cooking. There was a 71% reduction in the malondialdehyde concentration (0.52 ± 0.02 μ mol/250 g) in the meat of the spiced burgers compared with the malondialdehyde concentration (1.79 ± 0.17 μ mol/250 g) in the meat of the control burgers. The plasma malondialdehyde concentration increased significantly in the control burger group compared to the baseline ($p = 0.026$). There was a significant time-trend difference ($p = 0.013$) between the two groups. Urinary malondialdehyde concentrations (μ mol/g creatinine) decreased by 49% ($p = 0.021$) in subjects consuming the spiced burgers compared with subjects consuming the control burgers. The authors concluded that cooking hamburgers with a polyphenol-rich spice mixture can significantly decrease the concentration of malondialdehyde, suggesting potential health benefits for atherogenesis and carcinogenesis.

Nasal polyposis is a mucosal inflammatory disease that was investigated in a double-blind placebo-controlled crossover trial using 1 cup of a mint tea high in RA (about 300 mg) versus 1 cup of a mint tea low in RA (about 20 mg per day). Each treatment period lasted 4 weeks, separated by a 4-week washout period, and the first treatment followed a 2-week baseline period. Twenty-two adult subjects completed the study, and the authors found no statistically significant difference between the treatments in nasal stuffiness, as recorded on daily diary cards, in peak nasal inspiratory flows measured twice daily, or in patients' global assessment (including ability to smell or sleep) performed at the end of each treatment period [186].

A more recent randomized, parallel-arm, double-blind study (meeting the CONSORT statement) investigated the effect of RA in the management of knee osteoarthritis symptoms using tea brewed from the high-RA spearmint plant (130–150 mg of RA per cup, $n = 22$) and a commercially available spearmint tea (ca 13 mg of RA, $n = 24$). The subjects were instructed to consume two cups of tea per day from a 300-mL study mug provided to them, for a 16-week period. The outcome was measured using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain score, which is a validated, standardized 24-item questionnaire that assesses pain, disability, and joint stiffness as-

sociated with osteoarthritis. The study allowed the subjects to maintain their normal pain medication in order to explore the potential of the high-RA tea as a complementary therapy. The authors concluded that individuals who consumed 600 mL of high-RA spearmint tea daily showed a significant decrease in pain scores from weeks 0 to 16, inferring that adults with knee osteoarthritis may benefit from the inclusion of high-RA spearmint tea in their daily diet. No serious adverse events were reported during the study [187].

Clinical studies with isolated rosmarinic acid

RA was clinically investigated in atopic dermatitis due to its *in vitro* and *in vivo* anti-inflammatory effects, such as its ability to block complement fixation, inhibit lipoxygenase and cyclooxygenase activity, and suppress IKK- β downstream signaling in the TNF- α -induced upregulation of CCL11. Oil-in-water cream with or without rosmarinic acid (0.3%) was applied to the elbow flexures of 21 subjects (14 women and seven men; 15.1 ± 3.1 years) twice daily, for 4 and 8 weeks. The subjects were clinically graded as having moderate atopic dermatitis, according to the guidelines of the SCORAD index. The evaluation methods included clinical assessments (SCORAD), instrumental assessments (TEWL) and self-assessments by questionnaire. The authors reported that RA cream caused no reactions in the patch test on patient, suggesting that RA can safely be applied to human skin. After treatment with RA, the authors observed a statistically significant reduction in the SCORAD score, a decrease in itching, and a decrease in TEWL, suggesting that RA is a possible atopic dermatitis-mitigating agent [188].

Likewise, considering that RA is a strong anti-inflammatory agent in several animal models, a 21-day randomized controlled trial was undertaken to determine whether oral RA supplementation [200 mg ($n = 10$) or 50 mg ($n = 9$)] is an effective intervention for patients with seasonal allergic rhinoconjunctivitis. The patients recorded their symptoms daily in a diary card, and profiles of infiltrating cells, concentrations of eotaxin, IL-1 β , IL-8, and histamine in nasal lavage fluid, as well as serum IgE concentrations, were measured. The authors found that RA supplementation resulted in a significant increase in responder rates for itchy nose, watery eyes, itchy eyes, and overall symptoms ($p < 0.05$). Additionally, the treatment significantly decreased the numbers of neutrophils and eosinophils in nasal lavage fluid, compared to placebo supplementation. Patients reported no adverse events, and no significant abnormalities were detected in routine blood tests [189].

Pharmacokinetics in Humans

Pharmacokinetic studies designed for healthy volunteers have been described. A randomized, open-label, single-dose study investigated the PK parameters of RA and other depside salts after intravenous infusion in 12 volunteers (6 male, 6 female) divided into two groups, randomly receiving either 100 or 200 mg of RA. The authors described no significant differences in the PK parameters between male and female subjects. Three undetermined metabolites were found in the plasma at low concentrations. The urinary excretion recoveries of RA were 25.21% (20.61%) for the 100 mg dose, and 20.11% (10.50%) for the 200 mg dose. No adverse events were reported by the subjects or found by the investigators [190]. In a crossover design, a PK study with six healthy male volunteers with a 10-day washout period between

the administration of *P. frutescens* extract in a tablet containing 20% RA and placebo was carried out. The authors found that RA reached a maximum concentration in plasma after 0.5 h, followed by a gradual increase in the plasma concentration of methyl-RA, which reached a peak by 2 h. Approximately 75% of the total RA metabolites were then excreted in the urine within 6 h. These results showed that RA contained in *P. frutescens* extract was rapidly absorbed, subsequently methylated, and then excreted in the urine, and the majority of RA and its metabolites were present in the plasma as conjugated forms. The main metabolites found in the urine after consuming *P. frutescens* extract were sulfoglucuronide conjugates of RA and methyl-RA, indicating that conjugation of polyphenolic substances, either by glucuronidation and/or sulfation, occurs in human tissues such as the intestine and liver [191]. In comparative studies, Nakazawa and Ohsawa [192,193] found differences between human and rat metabolites of RA, reporting that RA may be predominantly metabolized to trimethoxycinnamic acid monoglucuronide in humans through hydrolytic cleavage in the gut, whereas in rats, RA is mainly metabolized to sulfated forms of *trans*-caffeic, ferulic, and *m*-coumaric acids.

Pharmacokinetics in Animals

Pharmacokinetic studies have been conducted in rats. Azevedo et al. showed that RA can modulate the transit of the intestinal Na⁺/glucose cotransporter-1 (SGLT-1) to the brush-border membrane, an effect that may contribute to the control of plasma glucose levels in diabetic rats [194]. Additionally, Debersac et al. showed that supplementation of a rat diet with 0.5% RA for 2 weeks did not increase the liver cytochrome P450 enzyme levels [195].

Konishi et al. compared PK parameters of caffeic acid and RA after oral administration in rats, indicating that the absorption efficiency of caffeic acid was higher than that of RA, and that the conjugation of both compounds occurs during permeation across the rat epithelium [196]. These findings are in accordance with Baba et al., which demonstrated that RA was rapidly absorbed (plasma values ca. 5 μ mol/L) and metabolized into conjugated and/or methylated forms, and a large amount of the absorbed RA was degraded and metabolized as conjugated forms of caffeic, ferulic, and *m*-coumaric acids [197].

Two studies on the development of the LC-MS/MS method and its application to PK studies of RA in rats found similar values for RA PK parameters, such as $C_{\max}$ (48.67 ± 11.24 [198] and 37.19 ± 13.85 ng/mL [199]) and $T_{\max}$ (1.08 ± 0.38 and 0.74 ± 0.12 h [199]), despite using different mathematical methods and doses. In [198], Drug and Statistics (DAS) 2.0 software (non-compartmental), and in [199], the practical pharmacokinetic program version 87 (3P87) (survival square sum) were used, with a single administration of Herba Isodi Rubescentis extract containing RA 2.55 mg/kg in [198], and in [199], a mixture of the standards in saline, with RA at 6.39 mg/kg.

Pharmaceutical Development

Focusing on the potential antioxidant activity of RA, technological studies were conducted with the aim of improving stability and bioavailability, and verifying antioxidant interactions. The incorporation of RA into formulas as an active component was al-

so proposed. In order to overcome the limitations of RA for cosmetic purposes, such as its low water solubility and discoloration, polycaprolactone microspheres loaded with RA were developed. RA-polycaprolactone microspheres with zwitterionic and non-ionic surfactants presented better loading efficiency when 10 mg of RA was incorporated. The microspheres showed better long-term stability in a cream formulation compared to RA alone [200]. In another study, solid lipid nanoparticles loaded with RA were prepared with the same objectives, resulting in better stability, which can be useful for applications in the food industry [201]. Also with the aim of increasing stability and water solubility, the cyclodextrin (β -CD) complexation of RA improved the properties and antioxidant capacity [202,203]. To study the interactions with α -tocopherol, the antioxidant efficiency of RA and RA-esters in oil-water emulsions was measured. All combinations resulted in improved antioxidant activity when compared to isolated compounds, since the concentrations were higher, and the combination of α -tocopherol and RA presented a synergistic effect. According to the authors, the formation of caffeic acid from RA in the presence of α -tocopherol occurred, and this conversion provided additional antioxidant outcomes [204]. RA proposed as an active compound against *Acne vulgaris* has been incorporated in a niosomal gel tested *in vivo* (Swiss albino mice). Both plain and niosomal formulations inhibited inflammation, and only the niosomal gel reduced the bacterial multiplication rate 4 days after application, due to prolonged release [205]. Also, considering the anti-inflammatory potential of RA, a preparation of a polygalacturonic/RA biodegradable membrane was developed to prevent postoperative abdominal adhesion, and was evaluated *in vitro* and *in vivo*. The authors demonstrated that this membrane could effectively inhibit adhesion as well as acute and chronic inflammation in rats [206].

Focusing on the construction of biosensors with high analytical performance, RA was used as a model for the quantification of pharmaceutical samples in an optimized biosensor synthesized with gold nanoparticles in an ionic liquid phase, supported in a biopolymeric matrix. The developed biosensor offered good precision and accuracy for the determination of RA [207]. In another study, RA was used to generate and stabilize gold and silver nanoparticles, acting as an appropriate antioxidant, being able to reduce the metallic ions, and also acting as a surface-passivation agent [208].

Concluding Remarks

RA is a natural metabolite that has attracted the interest of researchers in various areas of knowledge due to its abundance and potential biological properties. Analytical, biological, and technological RA data are compiled here for the first time. It has served as a model for a series of scientific proposals, and will continue to be a target of investigations and the production of knowledge. There is still much that needs to be done to ensure the data from nonclinical to clinical trials are translated into meaningful knowledge. There is a lack of connectivity between studies, and many gaps are yet to be filled in order to authenticate the role of RA in human health. In future investigations covering RA, translational research should be accomplished: the application of the findings generated during laboratory or preclinical research to the development of trials and studies in humans, furnishing promising new treatments with practical applications.

Methodology

Relevant articles from the literature were collected by searching the main scientific databases including Pubmed, Scopus, Scifinder, Web of Science, and Science Direct from 1990–2015, limiting the search to the occurrence of the keywords “Rosmarinic acid” in the title. This preliminary search identified more than 800 articles, which after the initial screening and removal of duplicates was refined, resulting in 281 articles that were scrutinized to compose this review.

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Conflict of Interest

The authors declare no conflicts of interest.

References

- 1 Khojasteh A, Mirjalili MH, Hidalgo D, Corchete P, Palazon J. New trends in biotechnological production of rosmarinic acid. *Biotechnol Lett* 2014; 36: 2393–2406
- 2 Petersen M. Rosmarinic acid: new aspects. *Phytochem Rev* 2013; 12: 207–227
- 3 Bulgakov VP, Inyushkina YV, Fedoreyev SA. Rosmarinic acid and its derivatives: biotechnology and applications. *Crit Rev Biotechnol* 2012; 32: 203–217
- 4 Petersen M, Abdullah Y, Benner J, Eberle D, Gehlen K, Hücherig S, Janiak V, Kim KH, Sander M, Weitzel C. Evolution of rosmarinic acid biosynthesis. *Phytochemistry* 2009; 70: 1663–1679
- 5 Park SU, Uddin R, Xu H, Kim YK, Lee SY. Biotechnological applications for rosmarinic acid production in plant. *Afr J Biotechnol* 2008; 7: 4959–4965
- 6 Petersen M, Simmonds MS. Rosmarinic acid. *Phytochemistry* 2003; 62: 121–125
- 7 Akowuah GA, Ismail Z, Norhayati I, Sadikun A. The effects of different extraction solvents of varying polarities on polyphenols of *Orthosiphon stamineus* and evaluation of the free radical-scavenging activity. *Food Chem* 2005; 93: 311–317
- 8 Zu G, Zhang R, Yang L, Ma C, Zu Y, Wang W, Zhao C. Ultrasound-assisted extraction of carnolic acid and rosmarinic acid using ionic liquid solution from *Rosmarinus officinalis*. *Int J Mol Sci* 2012; 13: 11027–11043
- 9 Dent M, Dragovic-Uzelac V, Penic M, Brncic M, Bosiljkov T, Levaj B. The effect of extraction solvents, temperature and time on the composition and mass fraction of polyphenols in Dalmatian wild sage (*Salvia officinalis* L.) extracts. *Food Technol Biotechnol* 2013; 51: 84–91
- 10 Argoti JC, Linares-Palomino PJ, Salido S, Ramirez B, Insuasty B, Altarejos J. On-line activity screening for radical scavengers from *Baccharis chilco*. *Chem Biodivers* 2013; 10: 189–197
- 11 Satake T, Kamiya K, Saiki Y, Hama T, Fujimoto U, Kitanaka S, Kimura Y, Uzawa J, Endang H, Umar M. Studies on the constituents of fruits of *Helicteres isora* L. *Chem Pharm Bull* 1999; 47: 1444–1447
- 12 de Oliveira KB, de Oliveira BH. HPLC/DAD determination of rosmarinic acid in *Salvia officinalis*: sample preparation optimization by factorial design. *J Braz Chem Soc* 2013; 24: 85–91
- 13 Wang L, Wang S, Yang S, Guo X, Lou H, Ren D. Phenolic alkaloids from the aerial parts of *Dracocephalum heterophyllum*. *Phytochemistry* 2012; 82: 166–171
- 14 Takeda Y, Oiso Y, Masuda T, Honda G, Otsuka H, Sezik E, Yesilada E. Iridoid and eugenol glycosides from *Nepeta cadmea*. *Phytochemistry* 1998; 49: 787–791
- 15 Wang MF, Li JG, Rangarajan M, Shao Y, LaVoie EJ, Huang TC, Ho CT. Antioxidative phenolic compounds from sage (*Salvia officinalis*). *J Agric Food Chem* 1998; 46: 4869–4873
- 16 Adham AN. Comparative extraction methods, phytochemical constituents, fluorescence analysis and HPLC validation of rosmarinic acid con-

- tent in *Mentha piperita*, *Mentha longifolia* and *Osimum basilicum*. J Pharmacogn Phytochem 2015; 3: 130–139
- 17 Abdullah Y, Schneider B, Petersen M. Occurrence of rosmarinic acid, chlorogenic acid and rutin in *Marantaceae* species. Phytochem Lett 2008; 1: 199–203
 - 18 Aritomi M, Kumori T, Kawasaki T. Cyanogenic glycosides in leaves of *Perilla-frutescens* var. *acuta* (Chemical studies on the constituents of edible plants, Part 4). Phytochemistry 1985; 24: 2438–2439
 - 19 Ondrejovič M, Benkovičová H, Šilhár S. Optimization of rosmarinic acid extraction from lemon balm (*Melissa officinalis*). Nova Biotechnol 2009; 9–2: 175–182
 - 20 Zibetti A, Aydi A, Livia M, Bolzan A, Barth D. Solvent extraction and purification of rosmarinic acid from supercritical fluid extraction fractionation waste: Economic evaluation and scale-up. J Supercrit Fluids 2013; 83: 133–145
 - 21 Angelov G, Penchev P, Condoret JS. Extraction of rosmarinic acid from botanicals with supercritical carbon dioxide. Effect of the modifiers added to the solvent. C R Acad Bulg Sci 2011; 64: 953–958
 - 22 Ho SK, Tan CP, Thoo YY, Abas F, Ho CW. Ultrasound-assisted extraction of antioxidants in Misai Kucing (*Orthosiphon stamineus*). Molecules 2014; 19: 12640–12659
 - 23 Dragović-Uzelac V, Garofulić IE, Jukić M, Penić M, Dent M. The influence of microwave-assisted extraction on the isolation of sage (*Salvia officinalis* L.). Polyphenols. Food Technol Biotechnol 2012; 50: 377–383
 - 24 Hong E, Park KH, Kim GH. Phenolic-enriched fractions from *Perilla frutescens* var. *acuta*: Determining rosmarinic acid and antioxidant activity. J Food Biochem 2011; 35: 1637–1645
 - 25 Cserhádi T. Carbon-based sorbents in chromatography. New achievements. Biomed Chromatogr 2009; 23: 111–118
 - 26 Kouri G, Tsimogiannis D, Bardouki H, Oreopouliou V. Extraction and analysis of antioxidant components from *Origanum dictamnus*. Innov Food Sci Emerg Technol 2007; 8: 155–162
 - 27 Kim S, Yun EJ, Bak JS, Lee H, Lee SJ, Kim CT, Lee JH, Kim KH. Response surface optimised extraction and chromatographic purification of rosmarinic acid from *Melissa officinalis* leaves. Food Chem 2010; 121: 521–526
 - 28 Hossain MA, Salehuddin SM, Kabir MJ, Rahman SMM, Rupasinghe HPV. Sinensetin, rutin, 3'-hydroxy-5,6,7,4'-tetramethoxyflavone and rosmarinic acid contents and antioxidative effect of the skin of apple fruit. Food Chem 2009; 113: 185–190
 - 29 Sahin S, Aybastier O, Isik E. Optimisation of ultrasonic-assisted extraction of antioxidant compounds from *Artemisia absinthium* using response surface methodology. Food Chem 2013; 141: 1361–1368
 - 30 Hossain MB, Brunton NP, Martin-Diana AB, Barry-Ryan C. Application of response surface methodology to optimize pressurized liquid extraction of antioxidant compounds from sage (*Salvia officinalis* L.), basil (*Ocimum basilicum* L.) and thyme (*Thymus vulgaris* L.). Food Funct 2010; 1: 269–277
 - 31 Hossain MB, Brunton NP, Patras A, Tiwari B, O'Donnell CP, Martin-Diana AB, Barry-Ryan C. Optimization of ultrasound assisted extraction of antioxidant compounds from marjoram (*Origanum majorana* L.) using response surface methodology. Ultrason Sonochem 2012; 19: 582–590
 - 32 Herrero M, Arraez-Roman D, Segura A, Kennedler E, Gius B, Raggid MA, Ibanez E, Cifuentes A. Pressurized liquid extraction-capillary electrophoresis-mass spectrometry for the analysis of polar antioxidants in rosemary extracts. J Chromatogr A 2005; 1084: 54–62
 - 33 Liu F, Tian S. A rapid method for the determination of rosmarinic acid in *Cordia dichotoma* seeds using ultrasound-assisted extraction and high-performance liquid chromatography-tandem mass spectrometry. Res J Chem Environ 2013; 17: 145–152
 - 34 Paniwnyk L, Cai H, Albu S, Mason TJ, Cole R. The enhancement and scale up of the extraction of anti-oxidants from *Rosmarinus officinalis* using ultrasound. Ultrason Sonochem 2009; 16: 287–292
 - 35 Vicente G, Molina S, González-Vallinas M, García-Risco MR, Fornari T, Reglero G, De Molina AR. Supercritical rosemary extracts, their antioxidant activity and effect on hepatic tumor progression. J Supercrit Fluids 2013; 79: 101–108
 - 36 Lung I, Soran ML, Tudoran C, Marutoiu C. Effect of microwave irradiation on polyphenolic compounds from *Satureja hortensis* L. Cent Eur J Chem 2013; 11: 535–541
 - 37 Rodríguez-Rojas S, Visentin A, Maestri D, Cocero MJ. Assisted extraction of rosemary antioxidants with green solvents. J Food Eng 2012; 109: 98–103
 - 38 Liu T, Sui X, Zhang R, Yang L, Zu Y, Zhang L, Zhang Y, Zhang Z. Application of ionic liquids based microwave-assisted simultaneous extraction of carnolic acid, rosmarinic acid and essential oil from *Rosmarinus officinalis*. J Chromatogr A 2011; 1218: 8480–8489
 - 39 Ozyurek M, Bener M, Guclu K, Apak R. Antioxidant/antiradical properties of microwave-assisted extracts of three wild edible mushrooms. Food Chem 2014; 157: 323–331
 - 40 Orlowska M, Stanimirova I, Staszek D, Sajewicz M, Kowalska T, Waks-mundzka-Hajnos M. Optimization of extraction based on the thin-layer chromatographic fingerprints of common thyme. J AOAC Int 2014; 97: 1274–1281
 - 41 Miron TL, Herrero M, Ibanez E. Enrichment of antioxidant compounds from lemon balm (*Melissa officinalis*) by pressurized liquid extraction and enzyme-assisted extraction. J Chromatogr A 2013; 1288: 1–9
 - 42 Chatterjee A, Tandon S, Ahmad A. Comparative extraction and downstream processing techniques for quantitative analysis of rosmarinic acid in *Rosmarinus officinalis*. Asian J Chem 2014; 26: 4313–4318
 - 43 Peshev D, Peeva LG, Peev G, Baptista IIR, Boam AT. Application of organic solvent nanofiltration for concentration of antioxidant extracts of rosemary (*Rosmarinus officinalis* L.). Chem Eng Res Des 2011; 89: 318–327
 - 44 Peev G, Penchev P, Peshev D, Angelov G. Solvent extraction of rosmarinic acid from lemon balm and concentration of extracts by nanofiltration: Effect of plant pre-treatment by supercritical carbon dioxide. Chem Eng Res Des 2011; 89: 2236–2243
 - 45 Rahimi A, Hashemi P, Badiei A, Safdarian M, Rashidipour M. Microextraction of rosmarinic acid using CMK-3 nanoporous carbon in a packed syringe. Chromatographia 2013; 76: 857–860
 - 46 Hu SS, Cao W, Da JH, Dai HB, Cao J, Ye LH, Li XY, Chu C. Dispersive micro solid-phase extraction with graphene oxide for the determination of phenolic compounds in dietary supplements by ultra high performance liquid chromatography coupled with quadrupole time-of-flight tandem mass spectrometry. Food Anal Methods 2015; 8: 833–840
 - 47 Štěrbová D, Matějček D, Vlček J, Kubáň V. Combined microwave-assisted isolation and solid-phase purification procedures prior to the chromatographic determination of phenolic compounds in plant materials. Anal Chim Acta 2004; 513: 435–444
 - 48 Rijo P, Fale PL, Serralheiro ML, Simoes MF, Gomes A, Reis C. Optimization of medicinal plant extraction methods and their encapsulation through extrusion technology. Measurement 2014; 58: 249–255
 - 49 Cabana R, Silva LR, Valentao P, Viturro CI, Andrade PB. Effect of different extraction methodologies on the recovery of bioactive metabolites from *Satureja parvifolia* (Phil.) Epling (Lamiaceae). Ind Crops Prod 2013; 48: 49–56
 - 50 Dastmalchi K, Damien Dorman HJ, Laakso I, Hiltunen R. Chemical composition and antioxidative activity of Moldavian balm (*Dracocephalum moldavica* L.) extracts. LWT-Food Sci Technol 2007; 40: 1655–1663
 - 51 Bettaieb Rebey I, Kefi S, Bourgo S, Ouergemmi I, Ksouri R, Tounsi MS, Marzouk B. Ripening stage and extraction method effects on physical properties, polyphenol composition and antioxidant activities of cumin (*Cuminum cyminum* L.) seeds. Plant Foods Hum Nutr 2014; 69: 358–364
 - 52 Plánder S, Gontaru L, Blazics B, Veres K, Kéry Á, Kareth S, Simándi B. Major antioxidant constituents from *Satureja hortensis* L. extracts obtained with different solvents. Eur J Lipid Sci Technol 2012; 114: 772–779
 - 53 Hadolin M, Knez Ž, Bauman D. Concentration of rosmarinic acid with supercritical fluids. Kem Ind 2003; 52: 427–432
 - 54 Peng CH, Su JD, Chyau CC, Sung TY, Ho SS, Peng CC, Peng RY. Supercritical fluid extracts of rosemary leaves exhibit potent anti-inflammation and anti-tumor effects. Biosci Biotechnol Biochem 2007; 71: 2223–2232
 - 55 Carvalho RN jr., Moura LS, Rosa PTV, Meireles MAA. Supercritical fluid extraction from rosemary (*Rosmarinus officinalis*): kinetic data, extract's global yield, composition, and antioxidant activity. J Supercrit Fluids 2005; 35: 197–204
 - 56 Herrero M, Plaza M, Cifuentes A, Ibanez E. Green processes for the extraction of bioactives from rosemary: chemical and functional characterization via ultra-performance liquid chromatography-tandem mass spectrometry and *in-vitro* assays. J Chromatogr A 2010; 1217: 2512–2520
 - 57 Li Y, Wang N, Zhang M, Ito Y, Zhang H, Wang Y, Guo X, Hu P. Development of a method to extract and purify target compounds from medicinal plants in a single step: online hyphenation of expanded bed adsorption chromatography and countercurrent chromatography. Anal Chem 2014; 86: 3373–3379
 - 58 Zhu F, Asada T, Sato A, Koi Y, Nishiwaki H, Tamura H. Rosmarinic acid extract for antioxidant, antiallergic, and alpha-glucosidase inhibitory

- activities, isolated by supramolecular technique and solvent extraction from *Perilla* leaves. *J Agric Food Chem* 2014; 62: 885–892
- 59 Baskan S, Oztekin N, Erim FB. Determination of carnosic acid and rosmarinic acid in sage by capillary electrophoresis. *Food Chem* 2007; 101: 1748–1752
 - 60 Santhiago M, Peralta RA, Neves A, Micke GA, Vieira IC. Rosmarinic acid determination using biomimetic sensor based on purple acid phosphatase mimetic. *Anal Chim Acta* 2008; 613: 91–97
 - 61 Oztürk M, Duru ME, Ince B, Harmandar M, Topçu G. A new rapid spectrophotometric method to determine the rosmarinic acid level in plant extracts. *Food Chem* 2010; 123: 1352–1356
 - 62 Saltas D, Pappas CS, Daferera D, Tarantilis PA, Polissiou MG. Direct determination of rosmarinic acid in Lamiaceae herbs using diffuse reflectance infrared fourier transform spectroscopy (DRIFTS) and chemometrics. *J Agric Food Chem* 2013; 61: 3235–3241
 - 63 Jemia MB, Tundis R, Maggio A, Rosselli S, Senatore F, Menichini F, Bruno M, Kchouk ME, Loizzo MR. NMR-based quantification of rosmarinic and carnosic acids, GC-MS profile and bioactivity relevant to neurodegenerative disorders of *Rosmarinus officinalis* L. extracts. *J Funct Foods* 2013; 5: 1873–1882
 - 64 Stehfest K, Boese M, Kerns G, Piry A, Wilhelm C. Fourier transform infrared spectroscopy as a new tool to determine rosmarinic acid *in situ*. *J Plant Physiol* 2004; 161: 151–156
 - 65 Janicsak G, Haznagay-Radnai E, Engel R, Blunden G, Mathe I. TLC-densitometry of rosmarinic and caffeic acids in the evaluation of Lamiaceae species growing in Central Europe. *JPC-J Planar Chromat – Mod TLC* 2013; 26: 132–136
 - 66 Domlur Thyagaraj V, Koshy R, Kachroo M, Mayachari AS, Sawant LP, Balasubramaniam M. A validated RP-HPLC-UV/DAD method for simultaneous quantitative determination of rosmarinic acid and eugenol in *Ocimum sanctum* L. *Pharm Methods* 2013; 4: 1–5
 - 67 Tian WJ, Jia J, Zhao L, Lü L, Li YY, Zhang H, Zhang GQ. HPLC-MS in simultaneous determination of 4 compounds in Fuzhengpingxiao capsule: Gentiopicroside, liquiritin, rosmarinic acid and harpagoside. *Academic Journal of Second Military Medical University* 2011; 32: 524–527
 - 68 Couto RO, Conceicao EC, Chaul LT, Oliveira EMS, Alves SF, Rezende KR, Bara MTF, Paula JR. Validated HPLC-PDA method for rosmarinic acid quantification in rosemary. *Latin Am J Pharm* 2011; 30: 1951–1956
 - 69 Jirovsky D, Kosina P, Myslinova M, Styskala J, Ulrichova J, Simanek V. HPLC analysis of rosmarinic acid in feed enriched with aerial parts of *Prunella vulgaris* and its metabolites in pig plasma using dual-channel coulometric detection. *J Agric Food Chem* 2007; 55: 7631–7637
 - 70 Fecka I, Kowalczyk A, Cisowski W. Optimization of the separation of flavonoid glycosides and rosmarinic acid from *Mentha piperita* on HPTLC plates. *JPC-J Planar Chromat – Mod TLC* 2004; 17: 22–25
 - 71 Wang MF, Juliani R, Zhang L, Wu QL, Simon JE. Analysis of flavonoids and rosmarinic acid contents in different varieties of mint by HPLC and LC-MS methods. *Abstr Pap Am Chem S* 2003; 226: U68–U68
 - 72 Franzoi AC, Dupont J, Spinelli A, Vieira IC. Biosensor based on laccase and an ionic liquid for determination of rosmarinic acid in plant extracts. *Talanta* 2009; 77: 1322–1327
 - 73 Kamatou GPP, Chen W, Viljoen AM. Quantification of rosmarinic acid in *Salvia* species indigenous to South Africa by HPTLC. *JPC-J Planar Chromat – Mod TLC* 2012; 25: 403–408
 - 74 Coran SA, Mulas S, Mulinacci N. Crucial aspects of high performance thin layer chromatography quantitative validation. The case of determination of rosmarinic acid in different matrices. *J Chromatogr A* 2012; 1220: 156–161
 - 75 Berhow MA, Affum AO, Gyan BA. Rosmarinic acid content in antidiabetic aqueous extract of *Ocimum canum* sims grown in Ghana. *J Med Food* 2012; 15: 611–620
 - 76 Janicsak G, Mathe I, Miklossy-Vari V, Blunden G. Comparative studies of the rosmarinic and caffeic acid contents of Lamiaceae species. *Biochem Syst Ecol* 1999; 27: 733–738
 - 77 Janicsak G, Mathe I. Parallel determination of rosmarinic and caffeic acids by TLC-densitometry. *Chromatographia* 1997; 46: 322–324
 - 78 Nowakowska J. Normal and reversed-phase TLC determination of rosmarinic and valerenic acids. *JPC-J Planar Chromat – Mod TLC* 2004; 17: 149–153
 - 79 Nowakowska J, Marszalt M. Retention properties of rosmarinic and valerenic acids on an amino-modified hydrophilic layer. *JPC-J Planar Chromat – Mod TLC* 2003; 16: 369–373
 - 80 Bandoni D, Murkovic M, Venskutonis PR. Determination of rosmarinic acid in sage and borage leaves by high-performance liquid chromatography with different detection methods. *J Chromatogr Sci* 2005; 43: 372–376
 - 81 Shanmuga Sundaram R, Ramanathan M, Rajesh R, Sathesh B, Saravanan D. LC-MS quantification of rosmarinic acid and ursolic acid in the *Ocimum sanctum* Linn. leaf extract (Holy Basil, Tulsi). *J Liq Chromatogr Relat Technol* 2012; 35: 634–650
 - 82 Li X, Yu C, Sun W, Liu G, Jia J, Wang Y. Simultaneous determination of magnesium lithospermate B, rosmarinic acid, and lithospermic acid in beagle dog serum by liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom* 2004; 18: 2878–2882
 - 83 Trute A, Nahrstedt A. Separation of rosmarinic acid enantiomers by three different chromatographic methods (HPLC, CE, GC) and the determination of rosmarinic acid in *Hedera helix* L. *Phytochem Anal* 1996; 7: 204–208
 - 84 Exarchou V, Troganis A, Gerothanassis IP, Tsimidou M, Boskou D. Identification and quantification of caffeic and rosmarinic acid in complex plant extracts by the use of variable-temperature two-dimensional nuclear magnetic resonance spectroscopy. *J Agric Food Chem* 2001; 49: 2–8
 - 85 Soobrattee MA, Neergheen VS, Luximon-Ramma A, Aruoma OI, Bahorun T. Phenolics as potential antioxidant therapeutic agents: mechanism and actions. *Mutat Res* 2005; 579: 200–213
 - 86 Ahmadvand H, Khosrobeigi A, Nemati L, Boshtam M, Jafari N, Hosseini RH, Pournia Y. Rosmarinic acid prevents the oxidation of low density lipoprotein (LDL) *in vitro*. *J Biol Sci* 2012; 12: 301–307
 - 87 Fuhrman B, Volkova N, Rosenblat M, Aviram M. Lycopene synergistically inhibits LDL oxidation in combination with vitamin E, glabridin, rosmarinic acid, carnosic acid, or garlic. *Antioxid Redox Signal* 2000; 2: 491–506
 - 88 Tache A, Radu GL, Litescu SC. Assessment of role of rosmarinic acid in preventing oxidative process of low density lipoproteins. *Chem Pap* 2012; 66: 1166–1170
 - 89 Panya A, Kittipongpittaya K, Laguerre M, Bayrasy C, Lecomte J, Ville-neuve P, McClements DJ, Decker EA. Interactions between α -tocopherol and rosmarinic acid and its alkyl esters in emulsions: synergistic, additive, or antagonistic effect? *J Agric Food Chem* 2012; 60: 10320–10330
 - 90 Maheswarappa NB, Subbaiah V, Muthupalani M, Yamagani PK, Mohan K, Keshapaga UR, Asokan SV, Kalappurakkal RC. Antioxidant activity of carnosic acid and rosmarinic acid in raw and cooked ground chicken patties. *J Sci Food Agric* 2014; 94: 273–279
 - 91 Sanchez-Campillo M, Gabaldon JA, Castillo J, Benavente-Garcia O, Del Bano MJ, Alcaraz M, Vicente V, Alvarez N, Lozano JA. Rosmarinic acid, a photo-protective agent against UV and other ionizing radiations. *Food Chem Toxicol* 2009; 47: 386–392
 - 92 Murakami K, Haneda M, Qiao S, Naruse M, Yoshino M. Prooxidant action of rosmarinic acid: transition metal-dependent generation of reactive oxygen species. *Toxicol In Vitro* 2007; 21: 613–617
 - 93 Munoz-Munoz JL, Garcia-Molina F, Ros E, Tudela J, Garcia-Canovas F, Rodriguez-Lopez JN. Prooxidant and antioxidant activities of rosmarinic acid. *J Food Biochem* 2013; 37: 396–408
 - 94 Gil Ede S, Enache TA, Oliveira-Brett AM. Redox behaviour of verbasco-side and rosmarinic acid. *Comb Chem High Throughput Screen* 2013; 16: 92–97
 - 95 Popov AM, Osipov AN, Korepanova EA, Krivoschapko ON, Artyukov AA. [Study of antioxidant and membrane activity of rosmarinic acid using different model systems]. *Biophysics (Russian Federation)* 2013; 58: 607–615
 - 96 Fadel O, El Kirat K, Morandat S. The natural antioxidant rosmarinic acid spontaneously penetrates membranes to inhibit lipid peroxidation *in situ*. *BBA. Biomembranes* 2011; 1808: 2973–2980
 - 97 Fujimoto A, Masuda T. Antioxidation mechanism of rosmarinic acid, identification of an unstable quinone derivative by the addition of odourless thiol. *Food Chem* 2012; 132: 901–906
 - 98 Wu TT, Hwang BR, Cho EJ. Scavenging effect of extract from *Perilla frutescens* and rosmarinic acid from free radical and lipid peroxidation. *J Food Sci Nutr* 2011; 16: 224–229
 - 99 Pirker KF, Kay CW, Stolze K, Tunega D, Reichenauer T, Goodman B. Free radical generation in rosmarinic acid investigated by electron paramagnetic resonance spectroscopy. *Free Radic Res* 2009; 43: 47–57
 - 100 Qiao S, Li W, Tsubouchi R, Haneda M, Murakami K, Takeuchi F, Nisimoto Y, Yoshino M. Rosmarinic acid inhibits the formation of reactive oxy-

- gen and nitrogen species in RAW264.7 macrophages. *Free Radic Res* 2005; 39: 995–1003
- 101 Nakamura Y, Ohto Y, Murakami A, Ohigashi H. Superoxide scavenging activity of rosmarinic acid from *Perilla frutescens* Britton var. *acuta* f. *viridis*. *J Agric Food Chem* 1998; 46: 4545–4550
 - 102 Chen S, Fu Y, Wu R. Effects of rosmarinic acid on free radical production and lysosomal enzyme release from rat peritoneal neutrophils. *Acta Pharm Sin* 1999; 34: 881–885
 - 103 Lamaison JL, Petitjean-Freytet C, Carnat A. [Medicinal Lamiaceae with antioxidant properties, a potential source of rosmarinic acid]. *Pharm Acta Helv* 1991; 66: 185–188
 - 104 Lamaison JL, Petitjean-Freytet C, Duband F, Carnat AP. Rosmarinic acid content and antioxidant activity in French Lamiaceae. *Fitoterapia* 1991; 62: 166–171
 - 105 Toussaint JP, Kraml M, Nell M, Smith SE, Smith FA, Steinkellner S, Schmidler C, Vierheilig H, Novak J. Effect of *Glomus mosseae* on concentrations of rosmarinic and caffeic acids and essential oil compounds in basil inoculated with *Fusarium oxysporum* f.sp. *basilici*. *Plant Pathol* 2008; 57: 1109–1116
 - 106 Tobimatsu Y, Elumalai S, Grabber JH, Davidson CL, Pan X, Ralph J. Hydroxycinnamate conjugates as potential monolignol replacements: *in vitro* lignification and cell wall studies with rosmarinic acid. *ChemSusChem* 2012; 5: 676–686
 - 107 Qiang Z, Ye Z, Hauck C, Murphy PA, McCoy JA, Widrechner MP, Reddy MB, Hendrich S. Permeability of rosmarinic acid in *Prunella vulgaris* and ursolic acid in *Salvia officinalis* extracts across Caco-2 cell monolayers. *J Ethnopharmacol* 2011; 137: 1107–1112
 - 108 Konishi Y, Kobayashi S. Transepithelial transport of rosmarinic acid in intestinal Caco-2 cell monolayers. *Biosci Biotechnol Biochem* 2005; 69: 583–591
 - 109 Bel-Rhliid R, Crespy V, Page-Zoerker N, Nagy K, Raab T, Hansen CE. Hydrolysis of rosmarinic acid from rosemary extract with esterases and *Lactobacillus johnsonii* *in vitro* and in a gastrointestinal model. *J Agric Food Chem* 2009; 57: 7700–7705
 - 110 Falé PL, Ascensao L, Serralheiro MLM. Effect of luteolin and apigenin on rosmarinic acid bioavailability in Caco-2 cell monolayers. *Food Funct* 2013; 4: 426–431
 - 111 Lin YY, Chen P, Xu XJ. Investigation of rosmarinic acid inhibition towards UDP-glucuronosyltransferases (UGTs) isoforms. *Latin Am J Pharm* 2013; 32: 459–461
 - 112 Li FR, Fu YY, Jiang DH, Wu Z, Zhou YJ, Guo L, Dong ZM, Wang ZZ. Reversal effect of rosmarinic acid on multidrug resistance in SGC7901/Adr cell. *J Asian Nat Prod Res* 2013; 15: 276–285
 - 113 Xu Y, Xu G, Liu L, Xu D, Liu J. Anti-invasion effect of rosmarinic acid via the extracellular signal-regulated kinase and oxidation-reduction pathway in Ls174-T cells. *J Cell Biochem* 2010; 111: 370–379
 - 114 Anusuya C, Manoharan S. Antitumor initiating potential of rosmarinic acid in 7,12-dimethylbenz(a)anthracene-induced hamster buccal pouch carcinogenesis. *J Environ Pathol Toxicol Oncol* 2011; 30: 199–211
 - 115 Sharmila R, Manoharan S. Anti-tumor activity of rosmarinic acid in 7,12-dimethylbenz(a)anthracene (DMBA) induced skin carcinogenesis in Swiss albino mice. *Indian J Exp Biol* 2012; 50: 187–194
 - 116 Venkatachalam K, Gunasekaran S, Jesudoss VA, Namasivayam N. The effect of rosmarinic acid on 1,2-dimethylhydrazine induced colon carcinogenesis. *Exp Toxicol Pathol* 2013; 65: 409–418
 - 117 Karthikkumar V, Sivagami G, Vinothkumar R, Rajkumar D, Nalini N. Modulatory efficacy of rosmarinic acid on premalignant lesions and antioxidant status in 1,2-dimethylhydrazine induced rat colon carcinogenesis. *Environ Toxicol Pharmacol* 2012; 34: 949–958
 - 118 Karmokar A, Marczylo TH, Cai H, Steward WP, Gescher AJ, Brown K. Dietary intake of rosmarinic acid by ApcMin mice, a model of colorectal carcinogenesis: levels of parent agent in the target tissue and effect on adenoma development. *Mol Nutr Food Res* 2012; 56: 775–783
 - 119 Kim JH, Lee BJ, Kim JH, Yu YS, Kim MY, Kim KW. Rosmarinic acid suppresses retinal neovascularization via cell cycle arrest with increase of p21(WAF1) expression. *Eur J Pharmacol* 2009; 615: 150–154
 - 120 Velpandian T, Gupta P, Ravi AK, Sharma HP, Biswas NR. Evaluation of pharmacological activities and assessment of intraocular penetration of an ayurvedic polyherbal eye drop (Itone™) in experimental models. *BMC Complement Altern Med* 2013; 13: 1–12
 - 121 Furtado MA, Fernandes de Almeida LC, Furtado RA, Cunha WR, Tavares DC. Antimutagenicity of rosmarinic acid in Swiss mice evaluated by the micronucleus assay. *Mutat Res – Genet Toxicol Environ Mutagen* 2008; 657: 150–154
 - 122 De Oliveira NCD, Sarmento MS, Nunes EA, Porto CM, Rosa DP, Bona SR, Rodrigues G, Marroni NP, Pereira P, Picada JN, Ferraz ABE, Thiesen FV, Da Silva J. Rosmarinic acid as a protective agent against genotoxicity of ethanol in mice. *Food Chem Toxicol* 2012; 50: 1208–1214
 - 123 Wang SW, Liu XL, Yu ZY, Han QF, Cong YW. Protective effect of rosmarinic acid on γ ray-induced micronucleus in polychromatic erythrocytes of murine bone marrow cells. *J Int Pharm Res* 2011; 38: 381–384
 - 124 Ku SK, Yang EJ, Song KS, Bae JS. Rosmarinic acid down-regulates endothelial protein C receptor shedding *in vitro* and *in vivo*. *Food Chem Toxicol* 2013; 59: 311–315
 - 125 Yang EJ, Ku SK, Lee W, Lee S, Lee T, Song KS, Bae JS. Barrier protective effects of rosmarinic acid on HMGB1-induced inflammatory responses *in vitro* and *in vivo*. *J Cell Physiol* 2013; 228: 975–982
 - 126 Englberger W, Hadding U, Etschenberg E, Graf E, Leyck S, Winkelmann J, Parnham MJ. Rosmarinic acid – A new inhibitor of complement C3-convertase with antiinflammatory activity. *Int J Immunopharmacol* 1988; 10: 729–737
 - 127 Boonyarikpunchai W, Sukrong S, Towiwat P. Antinociceptive and anti-inflammatory effects of rosmarinic acid isolated from *Thunbergia laurifolia* Lindl. *Pharmacol Biochem Behav* 2014; 124: 67–73
 - 128 Youn J, Lee KH, Won J, Huh SJ, Yun HS, Cho WG, Paik DJ. Beneficial effects of rosmarinic acid on suppression of collagen induced arthritis. *J Rheumatol* 2003; 30: 1203–1207
 - 129 Oh HA, Park CS, Ahn HJ, Park YS, Kim HM. Effect of *Perilla frutescens* var. *acuta* Kudo and rosmarinic acid on allergic inflammatory reactions. *Exp Biol Med* 2011; 236: 99–106
 - 130 Chu X, Ci X, He J, Jiang L, Wei M, Cao Q, Guan M, Xie X, Deng X. Effects of a natural prolyl oligopeptidase inhibitor, rosmarinic acid, on lipopolysaccharide-induced acute lung injury in mice. *Molecules* 2012; 17: 3586–3598
 - 131 Costa RS, Brasil Carneiro TC, Cerqueira-Lima AT, Queiroz NV, Alcantara-Neves NM, Pontes-de-Carvalho LC, Vellozo EdS, Oliveira EJ, Figueiredo CA. *Ocimum gratissimum* Linn. and rosmarinic acid, attenuate eosinophilic airway inflammation in an experimental model of respiratory allergy to *Blomia tropicalis*. *Int Immunopharmacol* 2012; 13: 126–134
 - 132 Jang AH, Kim TH, Kim GD, Park CS. Administration of rosmarinic acid ameliorated DNFB-induced atopic dermatitis like symptoms in NC/Nga mice. *Toxicol Lett* 2010; 196: S196
 - 133 Jang AH, Kim TH, Kim GD, Kim JE, Kim HJ, Kim SS, Jin YH, Park YS, Park CS. Rosmarinic acid attenuates 2,4-dinitrofluorobenzene-induced atopic dermatitis in NC/Nga mice. *Int Immunopharmacol* 2011; 11: 1271–1277
 - 134 Jiang WL, Chen XG, Qu GW, Yue XD, Zhu HB, Tian JW, Fu FH. Rosmarinic acid protects against experimental sepsis by inhibiting proinflammatory factor release and ameliorating hemodynamics. *Shock* 2009; 32: 608–613
 - 135 Sanbongi C, Takano H, Osakabe N, Sasa N, Natsume M, Yanagisawa R, Inoue K, Kato Y, Osawa T, Yoshikawa T. Rosmarinic acid inhibits lung injury induced by diesel exhaust particles. *Free Radic Biol Med* 2003; 34: 1060–1069
 - 136 Swarup V, Ghosh J, Ghosh S, Saxena A, Basu A. Antiviral and anti-inflammatory effects of rosmarinic acid in an experimental murine model of Japanese encephalitis. *Antimicrob Agents Chemother* 2007; 51: 3367–3370
 - 137 Yun SY, Hur YG, Kang MA, Lee J, Ahn C, Won J. Synergistic immunosuppressive effects of rosmarinic acid and rapamycin *in vitro* and *in vivo*. *Transplantation* 2003; 75: 1758–1760
 - 138 Jung DY, Kim EY, Joo SY, Jae BP, Moon C, Sa HK, Sim EY, Joh JW, Choon HK, Kwon GY, Kim SJ. Prolonged survival of islet allografts in mice treated with rosmarinic acid and anti-CD154 antibody. *Exp Mol Med* 2008; 40: 1–10
 - 139 Aung HT, Nikai T, Komori Y, Nonogaki T, Niwa M, Takaya Y. Biological and pathological studies of rosmarinic acid as an inhibitor of hemorrhagic *Trimeresurus flavoviridis* (habu) venom. *Toxins (Basel)* 2010; 2: 2478–2489
 - 140 Aung HT, Nikai T, Niwa M, Takaya Y. Rosmarinic acid in *Argusia argentea* inhibits snake venom-induced hemorrhage. *J Nat Med* 2010; 64: 482–486
 - 141 Aung HT, Furukawa T, Nikai T, Niwa M, Takaya Y. Contribution of cinnamic acid analogues in rosmarinic acid to inhibition of snake venom induced hemorrhage. *Bioorg Med Chem* 2011; 19: 2392–2396
 - 142 Dos Santos JI, Santos-Filho NA, Soares AM, Fontes MRM. Crystallization and preliminary X-ray crystallographic studies of a Lys49-phospholipase A2 homologue from *Bothrops pirajai* venom complexed with

- rosmarinic acid. *Acta Crystallogr F Struct Biol Commun* 2010; 66: 699–701
- 143 Dos Santos JJ, Cardoso FF, Soares AM, Dal Pai Silva M, Gallacci M, Fontes MR. Structural and functional studies of a bothropic myotoxin complexed to rosmarinic acid: new insights into Lys49-PLA₂ inhibition. *PLoS One* 2011; 6: e28521
 - 144 Ticli FK, Hage LIS, Cambraia RS, Pereira PS, Magro AJ, Fontes MRM, Stabeli RG, Giglio JR, Franca SC, Soares AM, Sampaio SV. Rosmarinic acid, a new snake venom phospholipase A(2) inhibitor from *Cordia verbenacea* (Boraginaceae): antiserum action potentiation and molecular interaction. *Toxicol* 2005; 46: 318–327
 - 145 Parker-Cote JL, O'Rourke DP, Miller SN, Brewer KL, Rosenbaum MD, Meggs WJ. Trypsin and rosmarinic acid reduce the toxicity of *Micrurus fulvius* venom in mice. *Clin Toxicol (Phila)* 2014; 52: 118–120
 - 146 Rossi F, Jullian V, Pawlowicz R, Kumar-Roine S, Haddad M, Darius HT, Gaertner-Mazouni N, Chinain M, Laurent D. Protective effect of *Heliotropium foertherianum* (Boraginaceae) folk remedy and its active compound, rosmarinic acid, against a Pacific ciguatoxin. *J Ethnopharmacol* 2012; 143: 33–40
 - 147 Zou ZW, Xu LN, Tian JY. [Antithrombotic and antiplatelet effects of rosmarinic acid, a water-soluble component isolated from *Radix Salviae Miltiorrhizae* (Danshen)]. *Acta Pharm Sin* 1993; 28: 241–245
 - 148 Domitrović R, Potočnjak I, Crnčević-Orlić T, Škoda M. Nephroprotective activities of rosmarinic acid against cisplatin-induced kidney injury in mice. *Food Chem Toxicol* 2014; 66: 321–328
 - 149 Tian J, Jiang W, Hou J, Wu H. Effect of rosmarinic acid on puromycin aminonucleoside induced nephrosis in rats. *Toxicol Lett* 2006; 164: S228
 - 150 Tian J, Jiang W. Rosmarinic acid inhibits acute renal injury and cyst formation in cisplatin-treated rat kidney. *Toxicol Lett* 2006; 164: S265
 - 151 Makino T, Ono T, Muso E, Yoshida H, Honda G, Sasayama S. Inhibitory effects of rosmarinic acid on the proliferation of cultured murine mesangial cells. *Nephrol Dial Transplant* 2000; 15: 1140–1145
 - 152 Jeong HJ, Choi Y, Kim MH, Kang IC, Lee JH, Park C, Park R, Kim HM. Rosmarinic acid, active component of Dansam-Eum attenuates ototoxicity of cochlear hair cells through blockage of caspase-1 activity. *PLoS One* 2011; 6: e18815
 - 153 Jiang WL, Xu Y, Zhang SP, Hou J, Zhu HB. Effect of rosmarinic acid on experimental diabetic nephropathy. *Basic Clin Pharmacol Toxicol* 2012; 110: 390–395
 - 154 Tavafi M, Ahmadvand H. Effect of rosmarinic acid on inhibition of gentamicin induced nephrotoxicity in rats. *Tissue Cell* 2011; 43: 392–397
 - 155 Tavafi M, Ahmadvand H, Khalatbari A, Tamjidipoor A. Rosmarinic acid ameliorates diabetic nephropathy in uninephrectomized diabetic rats. *Iran J Basic Med Sci* 2011; 14: 275–283
 - 156 Alkam T, Nitta A, Itoh A, Mizoguchi H, Tsunekawa H, Mouri A, Noda Y, Nabeshima T. Rosmarinic acid protects against memory impairments induced by acute i.c.v. injection of A beta(25–35). *J Pharmacol Sci* 2006; 100: 147 p
 - 157 Karthik D, Viswanathan P, Anuradha CV. Administration of rosmarinic acid reduces cardiopathology and blood pressure through inhibition of p22phox NADPH oxidase in fructose-fed hypertensive rats. *J Cardiovasc Pharmacol* 2011; 58: 514–521
 - 158 Karthik D, Arunkumar E, Viswanathan P, Anuradha CV. Rosmarinic acid treatment alleviates fibrotic changes in the myocardium induced in a rat model of insulin resistance. *Asian Pac J Trop Dis* 2012; 2 (Suppl. 2): S920–S926
 - 159 Sotnikova R, Okruhlicova L, Vlkovicova J, Navarova J, Gajdacova B, Pivackova L, Fialova S, Krenek P. Rosmarinic acid administration attenuates diabetes-induced vascular dysfunction of the rat aorta. *J Pharm Pharmacol* 2013; 65: 713–723
 - 160 Rocha JP, Sepodes BM, Eduardo-Figueira M, Bronze R, Silva-Lima B, Mota-Filipe H. Rosmarinic acid reduces multiple organ failure in thermal injury and liver ischemia-reperfusion injury. *FASEB J* 2009; 23: 739.15
 - 161 Yang MD, Chiang YM, Higashiyama R, Asahina K, Mann DA, Mann J, Wang CC, Tsukamoto H. Rosmarinic acid and baicalin epigenetically derepress peroxisomal proliferator-activated receptor gamma in hepatic stellate cells for their antifibrotic effect. *Hepatology* 2012; 55: 1271–1281
 - 162 Fialova S, Sotnikova R, Nosalova V, Drabikova K, Tekelova D, Kotalova D, Granai D. Ex vivo protective effect of rosmarinic acid and *Mentha x villosa* water extract on tissue injury induced by ischaemia/reperfusion. *Planta Med* 2010; 76: 1278–1279
 - 163 Domitrović R, Škoda M, Vasiljev Marchesi V, Cvijanović O, Pernjak Pugel E, Štefan MB. Rosmarinic acid ameliorates acute liver damage and fibrogenesis in carbon tetrachloride-intoxicated mice. *Food Chem Toxicol* 2013; 51: 370–378
 - 164 Li GS, Jiang WL, Tian JW, Qu GW, Zhu HB, Fu FH. In vitro and in vivo antifibrotic effects of rosmarinic acid on experimental liver fibrosis. *Phytomedicine* 2010; 17: 282–288
 - 165 Osakabe N, Yasuda A, Natsume M, Sanbongi C, Kato Y, Osawa T, Yoshikawa T. Rosmarinic acid, a major polyphenolic component of *Perilla frutescens*, reduces lipopolysaccharide (LPS)-induced liver injury in D-galactosamine (D-GalN)-sensitized mice. *Free Radic Biol Med* 2002; 33: 798–806
 - 166 Mushtaq N, Schmatz R, Pereira LB, Ahmad M, Stefanello N, Vieira JM, Abdalla F, Rodrigues MV, Baldissarelli J, Pelinson LP, Dalenogare DP, Reichert KP, Dutra EM, Mulinacci N, Innocenti M, Bellumori M, Morsch VM, Schetinger MR. Rosmarinic acid prevents lipid peroxidation and increase in acetylcholinesterase activity in brain of streptozotocin-induced diabetic rats. *Cell Biochem Funct* 2014; 32: 287–293
 - 167 Luan H, Kan Z, Xu Y, Lv C, Jiang W. Rosmarinic acid protects against experimental diabetes with cerebral ischemia: relation to inflammation response. *J Neuroinflammation* 2013; 10: 28
 - 168 Wang J, Xu H, Jiang H, Du X, Sun P, Xie J. Neurorescue effect of rosmarinic acid on 6-hydroxydopamine-lesioned nigral dopamine neurons in rat model of Parkinson's disease. *J Mol Neurosci* 2012; 47: 113–119
 - 169 Nie H, Peng Z, Lao N, Wang H, Chen Y, Fang Z, Hou W, Gao F, Li X, Xiong L, Tan Q. Rosmarinic acid ameliorates PTSD-like symptoms in a rat model and promotes cell proliferation in the hippocampus. *Prog Neuro-psychopharmacol Biol Psychiatry* 2014; 51: 16–22
 - 170 Jin X, Liu P, Yang F, Zhang YH, Miao D. Rosmarinic acid ameliorates depressive-like behaviors in a rat model of CUS and up-regulates BDNF levels in the hippocampus and hippocampal-derived astrocytes. *Neurochem Res* 2013; 38: 1828–1837
 - 171 Tawaratsumida Y, Sunagawa M, Kaneki K, Kijima T, Yoshida Y, Yoshida N, Hisamitsu T. Effect of rosmarinic acid on social isolation stress in rats. *Jpn Pharmacol Ther* 2013; 41: 43–50
 - 172 Takeda H, Tsuji M, Miyamoto J, Matsumiya T. Rosmarinic acid and caffeic acid reduce the defensive freezing behavior of mice exposed to conditioned fear stress. *Psychopharmacology (Berl)* 2002; 164: 233–235
 - 173 Takeda H, Tsuji M, Miyamoto J, Matsumiya T. Caffeic acid, an active metabolite of rosmarinic acid, reduces the freezing behavior of mice exposed to conditioned fear stress. *J Pharm Sci* 2003; 91: 191P–191P
 - 174 Ito N, Yabe T, Gamo Y, Nagai T, Oikawa T, Yamada H, Hanawa T. Rosmarinic acid from *Perillae Herba* produces an antidepressant-like effect in mice through cell proliferation in the hippocampus. *Biol Pharm Bull* 2008; 31: 1376–1380
 - 175 Takeda H, Tsuji M, Matsumiya T, Kubo M. Identification of rosmarinic acid as a novel antidepressive substance in the leaves of *Perilla frutescens* Britton var. *acuta* Kudo (Perillae Herba). *Nihon Shinkei Seishin Yakurigaku Zasshi* 2002; 22: 15–22
 - 176 Takeda H, Tsuji M, Inazu M, Egashira T, Matsumiya T. Rosmarinic acid and caffeic acid produce antidepressive-like effect in the forced swimming test in mice. *Eur J Pharmacol* 2002; 449: 261–267
 - 177 Pereira P, Tysca D, Oliveira P, Brun LFD, Picada JN, Ardenghi P. Neurobehavioral and genotoxic aspects of rosmarinic acid. *Pharmacol Res* 2005; 52: 199–203
 - 178 Park DH, Park SJ, Kim JM, Jung WY, Ryu JH. Subchronic administration of rosmarinic acid, a natural prolyl oligopeptidase inhibitor, enhances cognitive performances. *Fitoterapia* 2010; 81: 644–648
 - 179 Shimojo Y, Kosaka K, Noda Y, Shimizu T, Shirasawa T. Effect of rosmarinic acid in motor dysfunction and life span in a mouse model of familial amyotrophic lateral sclerosis. *J Neurosci Res* 2010; 88: 896–904
 - 180 Van Dyke T, Braswell L, Offenbacher S. Inhibition of gingivitis by topical application of ebselen and rosmarinic acid. *Inflamm Res* 1986; 19: 376–377
 - 181 Ranjbar A, Khorami S, Safarabadi M, Shahmoradi A, Malekiran AA, Vakilian K, Mandegary A, Abdollahi M. Antioxidant activity of Iranian *Echium amoenum* Fisch & C.A. Mey flower decoction in humans: A cross-sectional before/after clinical trial. *Evid Based Complement Alternat Med* 2006; 3: 469–473
 - 182 Mehrabani M, Ghannadi A, Sajjadi E, Ghassemi N, Shams-Ardakani M. Toxic pyrrolizidine alkaloids of *Echium amoenum* Fisch. and Mey. *DARU* 2006; 14: 122–127
 - 183 Rodriguez-Mateos A, Rendeiro C, Bergillos-Meca T, Tabatabaee S, George TW, Heiss C, Spencer JP. Intake and time dependence of blueberry flavonoid-induced improvements in vascular function: a randomized, controlled, double-blind, crossover intervention study with

- mechanistic insights into biological activity. *Am J Clin Nutr* 2013; 98: 1179–1191
- 184 Li Z, Henning SM, Zhang Y, Zerlin A, Li L, Gao K, Lee RP, Karp H, Thames G, Bowerman S, Heber D. Antioxidant-rich spice added to hamburger meat during cooking results in reduced meat, plasma, and urine malondialdehyde concentrations. *Am J Clin Nutr* 2010; 91: 1180–1184
 - 185 Viigimaa M, Abina J, Zemstovskaya G, Tikhaze A, Kononova G, Kumskova E, Lankin V. Malondialdehyde-modified low-density lipoproteins as biomarker for atherosclerosis. *Blood Press* 2010; 19: 164–168
 - 186 Goronfolah L, Ferrie P, Schmuck M, Waserman S, Denburg J, Kott L, Keith P, Crawford L, Fletcher R. A double-blind, placebo-controlled, randomized, crossover trial of a mint tea high in rosmarinic acid in adults with nasal polyposis. *J Allergy Clin Immunol* 2009; 123: S202
 - 187 Connelly AE, Tucker AJ, Tulk H, Catapang M, Chapman L, Sheikh N, Yurchenko S, Fletcher R, Kott LS, Duncan AM. High-rosmarinic acid spearmint tea in the management of knee osteoarthritis symptoms. *J Med Food* 2014; 17: 1361–1367
 - 188 Lee J, Jung E, Koh J, Kim YS, Park D. Effect of rosmarinic acid on atopic dermatitis. *J Dermatol* 2008; 35: 768–771
 - 189 Osakabe N, Takano H, Sanbongi C, Yasuda A, Yanagisawa R, Inoue KI, Yoshikawa T. Anti-inflammatory and anti-allergic effect of rosmarinic acid (RA); inhibition of seasonal allergic rhinoconjunctivitis (SAR) and its mechanism. *Biofactors* 2004; 21: 127–131
 - 190 Jia JY, Lu YL, Li XC, Liu GY, Li SJ, Liu Y, Liu YM, Yu C, Wang YP. Pharmacokinetics of depside salts from *Salvia miltiorrhiza* in healthy Chinese volunteers: A randomized, open-label, single-dose study. *Curr Ther Res Clin Exp* 2010; 71: 260–271
 - 191 Baba S, Osakabe N, Natsume M, Yasuda A, Muto Y, Hiyoshi T, Takano H, Yoshikawa T, Terao J. Absorption, metabolism, degradation and urinary excretion of rosmarinic acid after intake of *Perilla frutescens* extract in humans. *Eur J Nutr* 2005; 44: 1–9
 - 192 Nakazawa T, Ohsawa K. Metabolites of orally administered *Perilla frutescens* extract in rats and humans. *Biol Pharm Bull* 2000; 23: 122–127
 - 193 Nakazawa T, Ohsawa K. Metabolism of rosmarinic acid in rats. *J Nat Prod* 1998; 61: 993–996
 - 194 Azevedo MF, Lima CF, Fernandes-Ferreira M, Almeida MJ, Wilson JM, Pereira-Wilson C. Rosmarinic acid, major phenolic constituent of Greek sage herbal tea, modulates rat intestinal SGLT1 levels with effects on blood glucose. *Mol Nutr Food Res* 2011; 55 (Suppl. 1): S15–S25
 - 195 Debersac P, Vernevauf MF, Amiot MJ, Suschetet M, Siess MH. Effects of a water-soluble extract of rosemary and its purified component rosmarinic acid on xenobiotic-metabolizing enzymes in rat liver. *Food Chem Toxicol* 2001; 39: 109–117
 - 196 Konishi Y, Hitomi Y, Yoshida M, Yoshioka E. Pharmacokinetic study of caffeic and rosmarinic acids in rats after oral administration. *J Agric Food Chem* 2005; 53: 4740–4746
 - 197 Baba S, Osakabe N, Natsume M, Terao J. Orally administered rosmarinic acid is present as the conjugated and/or methylated forms in plasma, and is degraded and metabolized to conjugated forms of caffeic acid, ferulic acid and *m*-coumaric acid. *Life Sci* 2004; 75: 165–178
 - 198 Ma B, Wang Y, Zhang Q, Liu Y, Li J, Xu Q, Ying H. Simultaneous determination of oridonin, ponidicin and rosmarinic acid from *Herba Isodi Rubescens* extract by LC–MS–MS in rat plasma. *J Chromatogr Sci* 2013; 51: 910–918
 - 199 Liu Y, Li X, Li Y, Wang L, Xue M. Simultaneous determination of danshensu, rosmarinic acid, cryptotanshinone, tanshinone IIA, tanshinone I and dihydrotanshinone I by liquid chromatographic–mass spectrometry and the application to pharmacokinetics in rats. *J Pharm Biomed Anal* 2010; 53: 698–704
 - 200 Kim HJ, Kim TH, Kang KC, Pyo HB, Jeong HH. Microencapsulation of rosmarinic acid using polycaprolactone and various surfactants. *Int J Cosmet Sci* 2010; 32: 185–191
 - 201 Campos DA, Madureira AR, Gomes AM, Sarmiento B, Pintado MM. Optimization of the production of solid Witepsol nanoparticles loaded with rosmarinic acid. *Colloids Surf B Biointerfaces* 2014; 115: 109–117
 - 202 Çelik SE, Özyürek M, Tufan AN, Güçlü K, Apak R. Spectroscopic study and antioxidant properties of the inclusion complexes of rosmarinic acid with natural and derivative cyclodextrins. *Spectrochim Acta A Mol Biomol Spectrosc* 2011; 78: 1615–1624
 - 203 Medronho B, Valente AJ, Costa P, Romano A. Inclusion complexes of rosmarinic acid and cyclodextrins: stoichiometry, association constants, and antioxidant potential. *Colloid Polym Sci* 2014; 292: 885–894
 - 204 Panya A, Kittipongpittaya K, Laguerre M, Bayrasy C, Lecomte J, Ville-neuve P, McClements DJ, Decker EA. Interactions between α -tocopherol and rosmarinic acid and its alkyl esters in emulsions: synergistic, additive, or antagonistic effect? *J Agric Food Chem* 2012; 60: 10320–10330
 - 205 Budhiraja A, Dhingra G. Development and characterization of a novel antiacne niosomal gel of rosmarinic acid. *Drug Deliv* 2015; 22: 723–730
 - 206 Lee MW, Yang TP, Peng HH, Chen JW. Preparation and characterization of polygalacturonic acid/rosmarinic acid membrane crosslinked by short chain hyaluronate for preventing postoperative abdominal adhesion. *Carbohydr Polym* 2012; 87: 1749–1755
 - 207 Brondani D, Zapp E, Vieira IC, Dupont J, Scheeren CW. Gold nanoparticles in an ionic liquid phase supported in a biopolymeric matrix applied in the development of a rosmarinic acid biosensor. *Analyst* 2011; 136: 2495–2505
 - 208 Sarkar A, Shukla SP, Adhikari S, Mukherjee T. Synthesis, stabilisation and surface modification of gold and silver nanoparticles by rosmarinic acid and its analogues. *Int J Nanotechnol* 2010; 7: 1027–1037
 - 209 Akowuah GA, Ismail Z, Norhayati I, Sadikun A. The effects of different extraction solvents of varying polarities on polyphenols of *Orthosiphon stamineus* and evaluation of the free radical-scavenging activity. *Food Chem* 2005; 93: 311–317
 - 210 Olah NK, Radu L, Mogosan C, Hanganu D, Gocan S. Phytochemical and pharmacological studies on *Orthosiphon stamineus* Benth. (Lamiaceae) hydroalcoholic extracts. *J Pharm Biomed Anal* 2003; 33: 117–123
 - 211 Geller F, Schmidt C, Gottert M, Fronza M, Schattel V, Heinzmann B, Werz O, Flores EM, Merfort I, Laufer S. Identification of rosmarinic acid as the major active constituent in *Cordia americana*. *J Ethnopharmacol* 2010; 128: 561–566
 - 212 Suwanchaikasem P, Chaichantipyuth C, Sukrong S. Antioxidant-guided isolation of rosmarinic acid, a major constituent from *Thunbergia laurifolia*, and its use as a bioactive marker for standardization. *Chiang Mai J Sci* 2014; 41: 117–127
 - 213 Abdullah Y, Schneider B, Petersen M. Occurrence of rosmarinic acid, chlorogenic acid and rutin in Marantaceae species. *Phytochem Lett* 2008; 1: 199–203
 - 214 Aquino R, Morelli S, Lauro MR, Abdo S, Saija A, Tomaino A. Phenolic constituents and antioxidant activity of an extract of *Anthurium versicolor* leaves. *J Nat Prod* 2001; 64: 1019–1023
 - 215 Lin YL, Chang YY, Kuo YH, Shiao MS. Anti-lipid-peroxidative principles from *Tournefortia sarmentosa*. *J Nat Prod* 2002; 65: 745–747
 - 216 Lu YR, Foo LY. Rosmarinic acid derivatives from *Salvia officinalis*. *Phytochemistry* 1999; 51: 91–94
 - 217 Arda N, Goren N, Kuru A, Pengsuparp T, Pezzuto JM, Qiu SX, Cordell GA. Saniculoid N from *Sanicula europaea* L. *J Nat Prod* 1997; 60: 1170–1173
 - 218 Yamamoto H, Sakakibara J, Nagatsu A, Sekiya K. Inhibitors of arachidonate lipoxygenase from defatted perilla seed. *J Agric Food Chem* 1998; 46: 862–865
 - 219 Lee S, Song IH, Lee JH, Yang WY, Oh KB, Shin J. Sortase A inhibitory metabolites from the roots of *Pulsatilla koreana*. *Bioorg Med Chem Lett* 2014; 24: 44–48
 - 220 Furukawa M, Makino M, Ohkoshi E, Uchiyama T, Fujimoto Y. Terpenoids and phenethyl glucosides from *Hyssopus cuspidatus* (Labiatae). *Phytochemistry* 2011; 72: 2244–2252
 - 221 Satake T, Kamiya K, Saiki Y, Hama T, Fujimoto U, Kitanaka S, Kimura Y, Uzawa J, Endang H, Umar M. Studies on the constituents of fruits of *Helicteres isora* L. *Chem Pharm Bull* 1999; 47: 1444–1447
 - 222 Wang GC, Li T, Deng FY, Li YL, Ye WC. Five new phenolic glycosides from *Hedyotis scandens*. *Bioorg Med Chem Lett* 2013; 23: 1379–1382
 - 223 Christ B, Kesselring K. Process for isolating rosmarinic acid from plants. US Patent 4354035 A; 1982
 - 224 Achamlale S, Rezzonico B, Grignon-Dubois M. Rosmarinic acid from beach waste: Isolation and HPLC quantification in *Zostera detritus* from Arcachon lagoon. *Food Chem* 2009; 113: 878–883
 - 225 Lembo S, Balato A, Gaudiello F, Gasparri F, Monfrecola G. Ellagic and rosmarinic acid: modulatory effect on cytokines/chemokines released by keratinocytes after ultraviolet B radiation. *J Invest Dermatol* 2011; 131: S106
 - 226 Lembo S, Balato A, Di Caprio R, Cirillo T, Giannini V, Gasparri F, Monfrecola G. The modulatory effect of ellagic acid and rosmarinic acid on ultraviolet-B-induced cytokine/chemokine gene expression in skin keratinocyte (HaCat) cells. *Biomed Res Int* 2014; 2014: 346793

- 227 Moon DO, Kim MO, Lee JD, Choi YH, Kim GY. Rosmarinic acid sensitizes cell death through suppression of TNF- α -induced NF- κ B activation and ROS generation in human leukemia U937 cells. *Cancer Lett* 2010; 288: 183–191
- 228 Huang N, Hauck C, Yum MY, Rizshsky L, Widrechner MP, McCoy JA, Murphy PA, Dixon PM, Nikolau BJ, Birt DF. Rosmarinic acid in *Prunella vulgaris* ethanol extract inhibits lipopolysaccharide-induced prostaglandin E2 and nitric oxide in RAW 264.7 mouse macrophages. *J Agric Food Chem* 2009; 57: 10579–10589
- 229 Zdarilova A, Svobodova A, Simanek V, Ulrichova J. *Prunella vulgaris* extract and rosmarinic acid suppress lipopolysaccharide-induced alteration in human gingival fibroblasts. *Toxicol In Vitro* 2009; 23: 386–392
- 230 Kim HK, Lee JJ, Lee JS, Park YM, Yoon TR. Rosmarinic acid down-regulates the LPS-induced production of monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 α (MIP-1 α) via the MAPK pathway in bone-marrow derived dendritic cells. *Mol Cells* 2008; 26: 583–589
- 231 Scheckel KA, Degner SC, Romagnolo DF. Rosmarinic acid antagonizes activator protein-1-dependent activation of cyclooxygenase-2 expression in human cancer and nonmalignant cell lines. *J Nutr* 2008; 138: 2098–2105
- 232 Lee J, Jung E, Kim Y, Park J, Hong S, Hyun CG, Park D, Kim YS. Rosmarinic acid as a downstream inhibitor of IKK- β in TNF- α -induced upregulation of CCL11 and CCR3. *Br J Pharmacol* 2006; 148: 366–375
- 233 Zhang JJ, Wang YL, Feng XB, Song XD, Lu WB. Rosmarinic acid inhibits proliferation and induces apoptosis of hepatic stellate cells. *Biol Pharm Bull* 2011; 34: 343–348
- 234 Xu Y, Jiang Z, Ji G, Liu J. Inhibition of bone metastasis from breast carcinoma by rosmarinic acid. *Planta Med* 2010; 76: 956–962
- 235 Xavier CPR, Lima CF, Fernandes-Ferreira M, Pereira-Wilson C. Induction of apoptosis and inhibition of proliferation in colon cancer cells by *Salvia fruticosa*, *Salvia officinalis* and rosmarinic acid. *Planta Med* 2008; 74: 942–943
- 236 Xavier CP, Lima CF, Fernandes-Ferreira M, Pereira-Wilson C. *Salvia fruticosa*, *Salvia officinalis*, and rosmarinic acid induce apoptosis and inhibit proliferation of human colorectal cell lines: the role in MAPK/ERK pathway. *Nutr Cancer* 2009; 61: 564–571
- 237 Hur YG, Yun YD, Won JW. Rosmarinic acid induces p56(lck)-dependent apoptosis in Jurkat and peripheral T cells via mitochondrial pathway independent from Fas/Fas ligand interaction. *J Immunol* 2004; 172: 79–87
- 238 Hur YG, Suh CH, Kim S, Won J. Rosmarinic acid induces apoptosis of activated T cells from rheumatoid arthritis patients via mitochondrial pathway. *J Clin Immunol* 2007; 27: 36–45
- 239 Huang SS, Zheng RL. Rosmarinic acid inhibits angiogenesis and its mechanism of action *in vitro*. *Cancer Lett* 2006; 239: 271–280
- 240 Kolettas E, Thomas C, Leneti E, Skoufos I, Mbatsi C, Sisoula C, Manos G, Evangelou A. Rosmarinic acid failed to suppress hydrogen peroxide-mediated apoptosis but induced apoptosis of Jurkat cells which was suppressed by Bcl-2. *Mol Cell Biochem* 2006; 285: 111–120
- 241 Vatter DA, Jang HD, Levin R, Shetty K. Synergism of cranberry phenolics with ellagic acid and rosmarinic acid for antitumorigenic and DNA protection functions. *J Food Biochem* 2006; 30: 98–116
- 242 Yoshida M, Fuchigami M, Nagao T, Okabe H, Matsunaga K, Takata J, Karube Y, Tsuchihashi R, Kinjo J, Mihashi K, Fujioka T. Antiproliferative constituents from Umbelliferae plants VII. Active triterpenes and rosmarinic acid from *Centella asiatica*. *Biol Pharm Bull* 2005; 28: 173–175
- 243 Alcaraz M, Alcaraz-Saura M, Achel DG, Olivares A, Antonio Lopez-Morata J, Castillo J. Radiosensitizing effect of rosmarinic acid in metastatic melanoma B16F10 cells. *Anticancer Res* 2014; 34: 1913–1921
- 244 Braid N, Matin A, Rossi F, Chinain M, Laurent D, Guillemin GJ. Neuroprotective effects of rosmarinic acid on ciguatera in primary human neurons. *Neurotox Res* 2014; 25: 226–234
- 245 Costa P, Sarmiento B, Goncalves S, Romano A. Protective effects of *Lavandula viridis* L'Her extracts and rosmarinic acid against H2O2-induced oxidative damage in A172 human astrocyte cell line. *Ind Crops Prod* 2013; 50: 361–365
- 246 Jeon YJ, Song KS, Han HJ, Park SH, Chang W, Lee MY. Rosmarinic acid inhibits chemical hypoxia-induced cytotoxicity in primary cultured rat hepatocytes. *Arch Pharm Res* 2014; 37: 907–915
- 247 Kim SJ, Um JY, Kim SH, Hong SH. Protective effect of rosmarinic acid is through regulation of inflammatory cytokine in cadmium-induced ototoxicity. *Am J Chin Med* 2013; 41: 391–404
- 248 Jeong HJ, Choi Y, Kim MH, Kang IC, Lee JH, Park C, Park R, Kim HM. Rosmarinic acid, active component of Dansam-Eum attenuates ototoxicity of cochlear hair cells through blockage of caspase-1 activity. *PLoS One* 2011; 6: e18815
- 249 Yang SY, Hong CO, Lee GP, Kim CT, Lee KW. The hepatoprotection of caffeic acid and rosmarinic acid, major compounds of *Perilla frutescens*, against t-BHP-induced oxidative liver damage. *Food Chem Toxicol* 2013; 55: 92–99
- 250 Du T, Li L, Song N, Xie J, Jiang H. Rosmarinic acid antagonized 1-methyl-4-phenylpyridinium (MPP+)-induced neurotoxicity in MES23.5 dopaminergic cells. *Int J Toxicol* 2010; 29: 625–633
- 251 Ren P, Jiang H, Li R, Wang J, Song N, Xu HM, Xie JX. Rosmarinic acid inhibits 6-OHDA-induced neurotoxicity by anti-oxidation in MES23.5 cells. *J Mol Neurosci* 2009; 39: 220–225
- 252 Furtado RA, De Araújo FRR, Resende FA, Cunha WR, Tavares DC. Protective effect of rosmarinic acid on V79 cells evaluated by the micronucleus and comet assays. *J Appl Toxicol* 2010; 30: 254–259
- 253 Fallarini S, Miglio G, Paoletti T, Minassi A, Amoruso A, Bardelli C, Brunelleschi S, Lombardi G. Clovamide and rosmarinic acid induce neuroprotective effects in *in vitro* models of neuronal death. *Br J Pharmacol* 2009; 157: 1072–1084
- 254 Lee HJ, Cho HS, Park E, Kim S, Lee SY, Kim CS, Kim DK, Kim SJ, Chun HS. Rosmarinic acid protects human dopaminergic neuronal cells against hydrogen peroxide-induced apoptosis. *Toxicology* 2008; 250: 109–115
- 255 Salimei PS, Marfe G, Di Renzo L, Di Stefano C, Giganti MG, Filomeni G, Ciriolo MR. The interference of rosmarinic acid in the DNA fragmentation induced by osmotic shock. *Front Biosci* 2007; 12: 1308–1317
- 256 Iuvone T, De Filippis D, Esposito G, D'Amico A, Izzo AA. The spice sage and its active ingredient rosmarinic acid protect PC12 cells from amyloid-beta peptide-induced neurotoxicity. *J Pharmacol Exp Ther* 2006; 317: 1143–1149
- 257 Psotova J, Svobodova A, Kolarova H, Walterova D. Photoprotective properties of *Prunella vulgaris* and rosmarinic acid on human keratinocytes. *J Photochem Photobiol B* 2006; 84: 167–174
- 258 Yan T, Yan FX, Zhou JM, Zhu BY, Gong YZ, Xu CX, Chi XL, Zhang HQ. Effect of rosmarinic acid against PC12 cell injuries induced by glutamate. *Chinese Pharmacological Bulletin* 2006; 22: 955–959
- 259 Gao LP, Wei HL, Zhao HS, Xiao SY, Zheng RL. Antiapoptotic and antioxidant effects of rosmarinic acid in astrocytes. *Pharmazie* 2005; 60: 62–65
- 260 Kim DS, Kim HR, Woo ER, Hong ST, Chae HJ, Chae SW. Inhibitory effects of rosmarinic acid on adriamycin-induced apoptosis in H9c2 cardiac muscle cells by inhibiting reactive oxygen species and the activations of c-Jun N-terminal kinase and extracellular signal-regulated kinase. *Biochem Pharmacol* 2005; 70: 1066–1078
- 261 Chlopickova S, Psotova A, Miletova P, Sousek J, Lichnovsky V, Simanek V. Chemoprotective effect of plant phenolics against anthracycline-induced toxicity on rat cardiomyocytes part II. Caffeic, chlorogenic and rosmarinic acids. *Phytother Res* 2004; 18: 408–413
- 262 Renzulli C, Galvano F, Pierdomenico L, Speroni E, Guerra MC. Effects of rosmarinic acid against aflatoxin B1 and ochratoxin-A-induced cell damage in a human hepatoma cell line (Hep G2). *J Appl Toxicol* 2004; 24: 289–296
- 263 Lee HJ, Jeong YI, Lee TH, Jung ID, Lee JS, Lee CM, Kim JI, Joo H, Lee JD, Park YM. Rosmarinic acid inhibits indoleamine 2,3-dioxygenase expression in murine dendritic cells. *Biochem Pharmacol* 2007; 73: 1412–1421
- 264 Ahn SC, Oh WK, Kim BY, Kang DO, Kim MS, Heo GY, Ahn JS. Inhibitory effects of rosmarinic acid on Lck SH2 domain binding to a synthetic phosphopeptide. *Planta Med* 2003; 69: 642–646
- 265 Kang SH, Park SH, Shim HS, Lee KH. Non-phosphopeptide inhibitor for Lck SH2 domain: Solid-phase synthesis and structure activity relationship of rosmarinic acid analogs. *Bull Korean Chem Soc* 2003; 24: 664–666
- 266 Won J, Hur YG, Hur EM, Park SH, Kang MA, Choi Y, Park C, Lee KH, Yun Y. Rosmarinic acid inhibits TCR-induced T cell activation and proliferation in an Lck-dependent manner. *Eur J Immunol* 2003; 33: 870–879
- 267 Kang MA, Yun SY, Won JW. Rosmarinic acid inhibits Ca2+-dependent pathways of T-cell antigen receptor-mediated signaling by inhibiting the PLC- γ 1 and Itk activity. *Blood* 2003; 101: 3534–3542
- 268 Sahu A, Rawal N, Pangburn MK. Inhibition of complement by covalent attachment of rosmarinic acid to activated C3b. *Biochem Pharmacol* 1999; 57: 1439–1446

- 269 Peake PW, Pussell BA, Martyn P, Timmermans V, Charlesworth JA. The inhibitory effect of rosmarinic acid on complement involves the C5 convertase. *Int J Immunopharmacol* 1991; 13: 853–857
- 270 Abedini A, Roumy V, Mahieux S, Biabiany M, Standaert-Vitse A, Rivière C, Sahpaz S, Bailleul F, Neut C, Hennebelle T. Rosmarinic acid and its methyl ester as antimicrobial components of the hydromethanolic extract of *Hyptis atrorubens* Poit. (Lamiaceae). *Evid Based Complement Alternat Med* 2013; 2013: 604536
- 271 Airoidi C, Sironi E, Dias C, Marcelo F, Martins A, Rauter AP, Nicotra F, Jimenez-Barbero J. Natural compounds against Alzheimer's disease: molecular recognition of a beta 1–42 peptide by *Salvia sclareoides* extract and its major component, rosmarinic acid, as investigated by NMR. *Chem Asian J* 2013; 8: 596–602
- 272 Marcelo F, Dias C, Martins A, Madeira PJ, Jorge T, Helena Florencio M, Javier Canada F, Cabrita EJ, Jimenez-Barbero J, Rauter AP. Molecular recognition of rosmarinic acid from *Salvia sclareoides* extracts by acetylcholinesterase: a new binding site detected by NMR spectroscopy. *Chem Eur J* 2013; 19: 6641–6649
- 273 Yin G, Li YM, Wei W, Jiang SH, Zhu DY, Du WH. Interactions of acetylcholinesterase with salvianolic acid B and rosmarinic acid from *Salvia miltiorrhiza* water extract investigated by NMR relaxation rate. *Chin Chem Lett* 2008; 19: 747–751
- 274 Slobodníková L, Fialová S, Hupková H, Grančai D. Rosmarinic acid interaction with planktonic and biofilm *Staphylococcus aureus*. *Nat Prod Commun* 2013; 8: 1747–1750
- 275 Lin L, Dong Y, Zhao H, Wen L, Yang B, Zhao M. Comparative evaluation of rosmarinic acid, methyl rosmarinate and pedalin isolated from *Rabdosia serra* (MAXIM.) HARA as inhibitors of tyrosinase and α -glucosidase. *Food Chem* 2011; 129: 884–889
- 276 Murata T, Miyase T, Yoshizaki F. Hyaluronidase inhibitory rosmarinic acid derivatives from *Meehania urticifolia*. *Chem Pharm Bull (Tokyo)* 2011; 59: 88–95
- 277 Ippoushi K, Yamaguchi Y, Itou H, Azuma K, Higashio H. Evaluation of inhibitory effects of vegetables and herbs on hyaluronidase and identification of rosmarinic acid as a hyaluronidase inhibitor in lemon balm (*Melissa officinalis* L.). *Food Sci Technol Res* 2000; 6: 74–77
- 278 Fale PL, Borges C, Amorim Madeira PJ, Ascensao L, Araujo MEM, Florencio MH, Serralheiro MLM. Rosmarinic acid, scutellarein 4'-methyl ether 7-O-glucuronide and (16S)-coleon E are the main compounds responsible for the antiacetylcholinesterase and antioxidant activity in herbal tea of *Plectranthus barbatus* ("falso boldo"). *Food Chem* 2009; 114: 798–805
- 279 Fale PLV, Araujo MEM, Ascensao L, Serralheiro MLM. Acetylcholinesterase inhibition by rosmarinic acid from *Plectranthus* (Lamiaceae) species. *Planta Med* 2008; 74: 960
- 280 Lee J, Kim YS, Park D. Rosmarinic acid induces melanogenesis through protein kinase A activation signaling. *Biochem Pharmacol* 2007; 74: 960–968
- 281 Kang HS, Kim HR, Byun DS, Park HJ, Cho JS. Rosmarinic acid as a tyrosinase inhibitors from *Salvia miltiorrhiza*. *Nat Prod Sci* 2004; 10: 80–84
- 282 McCue PP, Shetty K. Inhibitory effects of rosmarinic acid extracts on porcine pancreatic amylase *in vitro*. *Asia Pac J Clin Nutr* 2004; 13: 101–106
- 283 Simpol LR, Otsuka H, Ohtani K, Kasai R, Yamasaki K. Nitrile glucosides and rosmarinic acid, the histamine inhibitor from *Ehretia philippinensis*. *Phytochemistry* 1994; 36: 91–95