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

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- isolation and analysis
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- pharmaceutical development

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.

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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

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:	IκB kinase β
LC:	liquid chromatography
LPS:	lipopolysaccharide
MPLC:	medium performance liquid chromatography
MS:	mass spectrometry
NF-κB:	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

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

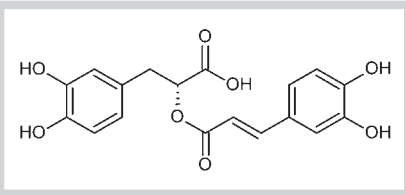

Fig. 1 (*R*)-(+)-rosmarinic acid.

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 µM) [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 ± 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 CO_2 with dimethyl ether demonstrated that dimethyl ether provided the highest RA yield [53]. The same plant leaves treated with supercritical fluid-CO_2 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 CO_2 and supercritical CO_2 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 ± 4.5% purity [58].

Analytical techniques used to determine RA include capillary electrophoresis [59], electromechanical [60], spectroscopical [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 preseparation 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
Orthosiphon stamineus leaves, (Lamiaceae) Malaysia [209]	Maceration	10 g	H_2O	40	2 h 4 h 8 h	5.40 6.61 6.71	HPLC equipped with a LiChrosorb RP-18 column (250 × 4.6 mm, 5 µm) and H_2O-MeOH-THF (45 : 50 : 5) as the mobile phase
			MeOH		2 h 4 h 8 h	5.41 6.48 7.99	
			H_2O-MeOH 1 : 1		2 h 4 h 8 h	9.03 9.78 9.54	
			$(CH_3)_2CO$-H_2O (3 : 7)		2 h 4 h 8 h	7.35 7.43 7.72	
Orthosiphon stamineus leaves, (Lamiaceae) Germany [210]	Maceration	100 g	EtOH-H_2O (1 : 1) EtOH-H_2O (3 : 7)	Room temperature	5 days	0.45 0.58	HPLC equipped with a guard column and LiChrosphere RP-18 column (125 × 4 mm, 5 µm). Eluent: gradient of H_3CCN-H_3PO_4 (99.9 : 0.1)/ H_2O-H_3PO_4 (98 : 2)
Salvia officinalis leaves, (Lamiaceae) USA [15]	Maceration	30 kg	EtOH-H_2O (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, Lichroprep RP-18 column using MeOH-H_2O (3 : 7), and EtOAc-MeOH-H_2O (12 : 1 : 1)
Salvia officinalis leaves, (Lamiaceae) Brazil [67]	Maceration	10 g	Aqueous ethanol	80		45–55	Extraction with $(Et)_2O$ fractionation with Chromatotron (centrifugal thin-layer chromatograph) eluted with EtOAc-hexane-AcOH (3 : 6 : 1)
Rosmarinus officinalis 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_3CN-H_2O (0.1 % formic acid).
				100		16.00 ± 0.98	
				150		16.78 ± 0.64	
				200		9.12 ± 0.34	
			H_2O	50		9.81 ± 0.89	
				100		14.19 ± 0.85	
				150		9.85 ± 0.38	
				200		8.60 ± 1.16	
Cordia americana 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_2O
						84.4	HPLC, LiChrosphere RP-18 column (5 × 100 mm; 5 µm), CH_3CN-H_2O gradient (0.1 % formic acid)
Thunbergia laurifolia leaves, (Acanthaceae) Thailand [212]	Maceration	20 g	EtOH-H_2O (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_2O-MeOH-AcOH (65 : 35 : 0.1)
Nakhon Pathom						38.80	
Nonthaburi Prakan						1.56	
Nakhon Sawan						14.86	
Prachin Buri						53.50	
Phetchabun						0.87	
Samut Prakan						3.01	

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
Mentha piperita leaves, (Lamiaceae) Iraq [16]	Maceration assisted by ultrasound	1 g	EtOH-H_2O (4:1)	40	1 h	1.43	HPLC instrument, C18 column (4.6 × 250 mm, 5 mm), isocratic MeOH-H_2O + 0.1 % AcOH (4:1)
Mentha longifolia leaves, (Lamiaceae) Iraq						2.08	
Osimum basilicum leaves, (Lamiaceae) Iraq						3.06	
Maranta depressa 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_3PO_4 used as the eluent
Maranta leuconeura ''Fascinator'' leaves, (Marantaceae) Germany						8.7	
Maranta leuconeura var. *kerchoviana* leaves, (Marantaceae) Germany						8.1	
Maranta leuconeura var. *massangeana* leaves, (Marantaceae) Germany						7.8	
Canna edulis leaves, (Cannaceae) Germany						37.2	
Canna indica leaves, (Cannaceae) Germany						50.7	
Perilla frutescens leaves, (Lamiaceae) Japan [18]	Maceration	650 g	MeOH	Room temperature		1.9	Acidification, amberlite column eluted with acidified H_2O and MeOH, droplet countercurrent chromatography eluted with $CHCl_3$-*n*-BuOH-MeOH-H_2O (9:2:12:8) and CC (Diaion HP20AG) eluted with H_2O-MeOH in gradient conditions
Melissa officinalis leaves, (Lamiaceae) Slovak [19]	Maceration		*i*PrOH-H_2O (39:61)	66	1 h	72.6 ± 3.1	HPLC analysis RP18, 250 × 4 mm, 5 µm, gradient condition of CH_3CN-H_2O, 0.1 % CF_3CO_2H
Anthurium versicolor 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_2O (1:1)
Tournefortia sarmentosa (Boraginaceae) Taiwan [215]	Maceration	20 kg	EtOH-H_2O (85:15)	50		0.625	Diaion HP-20 column chromatography using a gradient of MeOH-H_2O and Sephadex LH-20 using MeOH 80 %
Salvia officinalis (Lamiaceae) New Zealand [216]	Maceration	50 g	Me_2CO-H_2O (7:3)	Room temperature		48.65	Diaion HP-20 column, eluent H_2O then MeOH, Sephadex LH-20 column MeOH-H_2O (7:3), HPLC equipped with an RP-18 column elution gradient of CH_3CN-H_2O (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
Sanicula europaea aerial parts, (Apiaceae) Turkey [217]	Maceration	940 g	EtOH–H_2O (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_2O (61 : 32 : 7)
Perilla frutescens seeds, (Lamiaceae) Japan [218]	Extraction assisted by heating	800 g	EtOH	Reflux	2 h	0.024	Liquid-liquid extraction Hex, EtOAc-H_2O, EtOAc. Fraction purified by CC silica gel, Sephadex LH-20 and HPLC equipped with an ODS column, MeOH-H_2O (1 : 1) used as the eluent
Nepeta cadmea aerial parts, (Lamiaceae) Turkey [14]	Maceration	1.25 kg	MeOH	Room temperature	30 days	0.024	Liquid-liquid extraction Hex-MeOH, H_2O-(EtOAc, *n*-BuOH). *n*-BuOH fraction purified with CC on Dianion HP-20 MeOH-H_2O 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_2O
Pulsatilla koreana roots, (Ranunculaceae) South Korea [219]	Maceration	1.2 kg	MeOH and CH_2Cl_2	Room temperature		0.017	Vacuum flash chromatography on RP-18 using MeOH and H_2O as the eluent in gradient condition. Further purification took place with reversed-phase HPLC (YMC-ODS column; H_2O-MeOH gradient)
Hyssopus cuspidatus 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_2O acetone, silica gel CC eluted with $CHCl_3$-MeOH-H_2O reversed-phase HPLC with mobile phase MeOH-H_2O (2 : 6) and reversed-phase HPLC CH_3CN-H_2O (1 : 9) as the mobile phase
Baccharis chilco aerial parts, (Asteraceae) Colombia [10]	Extraction assisted by heating	446 g	CH_2Cl_2 and EtOH	Reflux	2 h	0.045	CC on silica gel with CH_2Cl_2-EtOH used as the eluent. H_2O (alkaline)-EtOAc separation and HPLC purification of the organic phase using isocratic the condition of MeOH-H_2O (2 : 3)
Helicteres isora fruits, (Sterculiaceae) Indonesia [221]	Extraction assisted by heating	4 kg	MeOH	Reflux 60	7 h	0.078	Liquid-liquid extraction $CHCl_3$-MeOH-H_2O (5 : 3 : 8) and then with EtOAc and *n*-BuOH. CC on Sephadex LH-20 using MeOH-H_2O (2 : 1) as th eluent. A second purification on Sephadex LH-20 eluted with MeOH-H_2O (2 : 1), followed by successive purification on an MPLC silica gel column and an RP-18 column eluted with EtOAc-MeOH-H_2O (60 : 25 : 15) and H_2O-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
Hedyotis scandens (Rubiaceae) [222]	Percolation	9 kg	EtOH 95 %	Room temperature		0.006	Liquid-liquid extraction H_2O, petroleum ether, EtOAc, and *n*-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
Melissa officinalis leaves, (Lamiaceae) [223]	Extraction assisted by stirring	100 g	Acidified H_2O	80–100	45 min	13	Liquid-liquid extraction with Et_2O, Sephadex LH-20 using MeOH-H_2O (7 : 3). Recrystallization at 4 °C
Zostera noltii leaves, (Zosteraceae) France [224]	Extraction assisted by heating	500 g	MeOH	Reflux		14.4	Liquid-liquid extraction $CHCl_3$, EtOAc and H_2O, 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_2O (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 milimolar, 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]. Antihemorrhagic, 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-κB), 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]. Cardioprotection [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, CCl_4, 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 µM	prevention of UVB-induced inflammation
Ku et al., 2013 [124]	ELISA (primary human umbilical vein endothelial cells)	0.1–2 µM	inhibition of endothelial protein C receptor shedding
Moon et al., 2010 [227]	Cell viability (U937 human leukemia cells)	15–60 µM	↓ TNF-α-induced ROS generation ↓ NF-κB activation ↑ TNF-α-induced apoptosis
Huang et al., 2009 [228]	LPS stimulation (RAW 264.7 mouse macrophage cells)	2.67 µM	↓ LPS-induced prostaglandin E2 and nitric oxide production
Zdarilová et al., 2009 [229]	LPS stimulation (primary cultured human gingival fibroblasts)	1 µg/mL	↓ oxidative damage ↓ inflammation
Kim et al., 2008 [230]	LPS inflammatory stimulation (BMDCs bone marrow-derived dendritic cells)	0.1–200 µM	↓ cell maturation and migration ↓ monocyte chemoattractant protein-1 ↓ macrophage inflammatory protein-1α
Scheckel et al., 2008 [231]	Luciferase assay (HT-29 colon cancer and MCF10 A non-malignant epithelial cells)	5–20 µM	↓ 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 µM IC_{50} = 9.1–15.8 µM	↓ 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 µg/mL IC_{50} = 7.1 µg/mL	↓ cell proliferation ↑ apoptosis
Xu et al., 2010 [113]	Wound healing, adhesion and Transwell assays (Ls174-T human colon carcinoma cells)	5–300 µg/mL IC_{50} < 20 µg/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 µg/mL	↓ tumoral cells migration (IC_{50} = 118 µg/mL) bone protection *in vitro*
Kim et al., 2009 [119]	Cell viability and morphological changes (HRMEC human retina microvascular endothelial cells)	10–100 µM	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 µM	↓ 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 µM	↓ cell proliferation ↑ apoptosis
Huang et al., 2006 [239]	Cell viability and migration assays (HUVEC human umbilical vein endothelial cells)	12.5–200 µM	↓ several steps of angiogenesis
Kolettas et al., 2006 [240]	Cell viability (Jurkat human T lymphoma cells)	10–150 µM	↓ cell proliferation ↑ apoptosis
Vattem et al., 2006 [241]	AMES and supercoiled DNA strand scission assay	500 µg/plate	antimutagenic effect
Yoshida et al., 2005 [242]	Cell viability (MK-1, HeLa, and B16F10 cells)	MK-1, GI_{50} = 119 µM HeLa, GI_{50} = 75 µM B16F10, GI_{50} = 16 µM	↓ cell proliferation
Cytoprotection			
Alcaraz et al., 2014 [243]	Micronucleus (human lymphocytes) Cell viability (PNT2 and B16F10 cells)	10–40 µM	radioprotection in normal cells ↑ radio-induced damage in melanoma cells
Braidy et al., 2014 [244]	Cell viability (primary cultured human neurons)	0.01–1 mg/mL	protection against ciguatoxin-induced neurotoxicity
Costa et al., 2013 [245]	Cell viability (A172 human astrocyte cells)	30 µg/mL	protection against H_2O_2-induced oxidative damage
Jeon et al., 2013 [246]	Cell viability (primary cultured rat hepatocytes)	1–100 µM	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 µM	protection against $Cd2^+$-induced or cisplatin-induced ototoxicity protection against cisplatin-induced destruction of hair cell arrays *ex vivo*
Yang et al., 2013 [249]	Cell viability (HepG2 human hepatoma cells)	10–26.84 µg/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 µM	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 µM EC_{50} = 0.9–3.7 µM	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 µM	protection against H_2O_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 µM	↓ sorbitol-induced apoptosis
Iuvone et al., 2006 [256]	Cell viability (PC12 adrenal medulla cells)	0.0036–36 µg/mL	↓ β-amyloid-induced cell death
Psotova et al., 2006 [257]	Cell viability (HaCaT human keratinocyte cells)	0.9–18 µg/mL	photoprotection against UVA-induced damage
Yan et al., 2006 [258]	Cell viability (PC12 cells)	100 µM	protection against glutamate-induced cell death ↓ apoptosis
Gao et al., 2005 [259]	Cell viability (primary cultured rat astrocytes)	10–40 µM	protection against H_2O_2-induced cell death ↓ apoptosis
Kim et al., 2005 [260]	Cell viability (H9c2 cardiomyoblast cells)	1–20 µg/mL	protection against adriamycin-induced apoptosis ↓ apoptosis
Chlopcikova et al., 2004 [261]	Cell viability (primary cultured rat cardiomyocytes)	100–200 µM	protection against doxorubicin-induced cell death ↓ lipid peroxidation (IC_{50} = 8.17 µM)
Renzulli et al., 2004 [262]	Cell viability (Hep G2 human hepatoma-derived cells)	2.5–100 µM	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 µM	↓ 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 µM IC_{50} = 5.6–14 µM	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 µM	↓ 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
Miscelaneous			
Abedini et al., 2013 [270]	Minimal inhibitory concentration/minimal bactericidal concentration by broth microdilution	0.0093–2.5 mg/mL	antimicrobial activity
Airoldi 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 µM 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 µg/mL	antimicrobial activity inactive as biofilm-eradicator
Yang et al., 2012 [161]	Cellular differentiation reversal (primary cultured hepatic stellate cells)	135–270 µM	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 µg/mL	antivenom effects *in vitro* and *ex vivo*
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 µM	hyaluronidase inhibition
Falé et al., 2008, 2009 [278, 279]	Enzymatic activity inhibition	IC_{50} = 440 µg/mL	acetylcholinesterase inhibition (Alzheimer's disease)
Lee et al., 2007 [280]	Melanin content determination (B16 melanoma cells)	1–100 µM	↑ melanogenesis
Kang et al., 2004 [281]	Enzymatic activity inhibition	IC_{50} = 16.8 µM	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 µg/mL IC_{50} = 1.4–3.8 µg/mL	↓ cell proliferation
Simpol et al., 1994 [283]	Histamine release inhibition (rat mast cells)	IC_{50} = 18 µM	↓ 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 major 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 µmol/250 g) in the meat of the spiced burgers compared with the malondialdehyde concentration (1.79 ± 0.17 µmol/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 (µmol/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 atopical 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 atopical 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 rhinoconjuctivitis. The patients recorded their symptoms daily in a diary card, and profiles of infiltrating cells, concentrations of eotaxin, IL-1β, 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 µmol/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 nonionic 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 synthetized 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 nanoparticules, 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.

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