REVIEW
Traditional Medicine Research 2025;10(8):50. https://doi.org/10.53388/TMR20241005001

Potential role of rosemary in cardiovascular disease therapies: progress and promise

Yu-Cheng Liang[1, 2], Tang-Jiang Wan[1, 2], Tian-Wen Wei[3], Jun Zhang[1, 2], Ya-Fei Li[1, 2, 4*]

[1]Department of Cardiology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou 215000, China. [2]Gusu School, Nanjing Medical University, Suzhou 215000, China. [3]Department of Cardiovascular Medicine, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai 200070, China. [4]Suzhou Key Laboratory of Cardiovascular Disease, Suzhou 215004, China.

[*]**Correspondence to:** Ya-Fei Li, Department of Cardiology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, No. 242, Guangji Road, Suzhou 215000, China. E-mail: dryafeili@njmu.edu.cn.

Author contributions

Liang YC, Wan TJ and Zhang J contributed significantly to query papers and paper analysis. Liang YC organized the data and wrote the manuscript. Wei TW helped perform the analysis with constructive discussions. Li YF designed, supervised the study, and performed the manuscript editing.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (82370287), Jiangsu Natural Science Foundation Project (No. BK20231204), the Medical Research Project of Jiangsu Provincial Health Commission (No. M2022042), the Suzhou Key Laboratory of Cardiovascular Disease (SZS2024015) and Suzhou Science and Technology Plan Project Medical Innovation Application Research (No. SKY2022188).

Peer review information

Traditional Medicine Research thanks all anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations

CVDs, cardiovascular diseases; ACE, angiotensin-converting enzyme; CA, carnosic acid; RA, rosmarinic acid; UA, ursolic acid; NADPH, (reduced) nicotinamide adenine dinucleotide phosphate; ET-1, endothelin-1; eNOS, endothelial nitric-oxide synthase; ROS, reactive oxygen species; AKT, protein kinase B; SOD, superoxide dismutase; NLRP3, nod-like receptor protein 3; Nrf2, nuclear factor erythroid-2 related factor 2; HO-1, heme oxygenase-1; TGF, transforming growth factor; AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; MAPK, mitogen-activated protein kinase; DCM, diabetic cardiomyopathy; NF-κB, nuclear factor κB; SREBP, sterol-regulatory element binding proteins; MI, myocardial infarction.

Citation

Liang YC, Wan TJ, Wei TW, Zhang J, Li YF. Potential role of rosemary in cardiovascular disease therapies: progress and promise. *Tradit Med Res*. 2025;10(8):50. doi: 10.53388/TMR20241005001.

Executive editor: Xin-Yue Zhang.

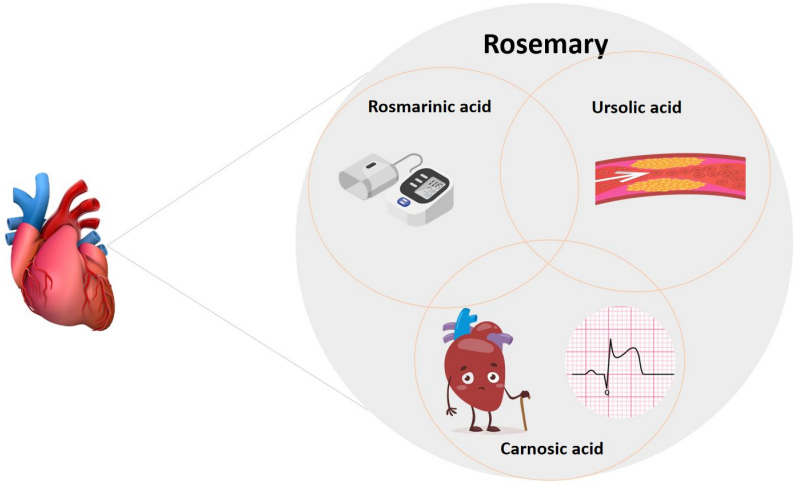
Received: 05 October 2024; **Revised:** 09 December 2024; **Accepted:** 20 February 2025; **Available online:** 24 February 2025.

© 2025 By Author(s). Published by TMR Publishing Group Limited. This is an open access article under the CC-BY license. (https://creativecommons.org/licenses/by/4.0/)

Abstract

Cardiovascular diseases (CVDs) rank among the foremost contributors to mortality worldwide. Despite the significant breakthroughs in treatment and drug development in recent years, the incidence and mortality rates associated with CVDs continue to remain alarmingly high. In terms of drugs, numerous medications often come with various adverse effects while they actually exert therapeutic effects. As economies grow and living standards improve, patients with CVDs increasingly seek medications with precise efficacy but minimal side effects. Recent evidence increasingly indicates the significant role of traditional Chinese medicine in the treatment of CVDs. Rosemary (*Rosmarinus officinalis* L.), a fragrant plant with medicinal properties, is extensively utilized in folk medicine, pharmaceuticals, and the cosmetics industry, with its safety extensively confirmed by research. As a potent antioxidant, its anti-oxidant and anti-inflammatory properties confer potential application value in treating various diseases, including CVDs. This paper reviews the applications and mechanisms of rosemary and its main active components in treating CVDs and systematically summarizes their effects in regulating blood pressure, combating myocardial ischemia, enhancing heart function, and preventing atherosclerosis, thereby offering a foundation for the development of novel treatment strategies.

Keywords: rosemary; pharmacokinetics; rosmarinic acid; carnosic acid; ursolic acid; cardiovascular disease



Traditional Medicine Research 2025;10(8):50. https://doi.org/10.53388/TMR20241005001

Highlights

Summarized the pharmacokinetic parameters of the main active ingredients in rosemary.

Evaluated the safety of rosemary active ingredients as drugs.

Elaborated on the progress and mechanism of rosemary in the treatment of cardiovascular diseases in recent years.

Medical history of objective

Rosemary, scientifically designated as *Rosmarinus officinalis* L., is a member of the Lamiaceae botanical family, hailing from the Mediterranean region. According to legend, the earliest records of rosemary can be traced back to cuneiform script dating to 5,000 B.C.E., as documented in Pliny the Elder's *Natural History* (70–77 C.E.) and Dioscorides' *De Materia Medica* (50–70 C.E.). Rosemary was introduced to China and disseminated worldwide at least 1,800 years ago. In traditional medicinal practices, rosemary is esteemed for its purported abilities to bolster memory, alleviate pain, and combat infections. Consequently, it is routinely utilized as a preventive and therapeutic measure against plagues and other contagious ailments. Modern pharmacology indicates that rosemary also has good efficacy in preventing and treating cardiovascular diseases.

Background: Rosemary and cardiovascular diseases (CVDs)

Cardiovascular ailments represent a substantial contributor to mortality rates among humans, accounting for approximately one-third of global deaths [1]. According to a report from the Ministry of Health of China, among chronic diseases, the prevalence rate (220.4‰) and mortality rate (165.37 per 100,000 people) of heart disease rank first among the population (http://www.nhc.gov.cn/mohwsbwstjxxzx/tjtjnj/202305/6ef68aac6bd14c1eb9375e01a0faa1fb/files/b05b3d958fc546d98261d165cea4adba.pdf). Hypertension, smoking, diabetes, alcohol intake, obesity, blood lipids, diet, physical activity, and psychosocial factors are considered as risk factors for CVDs [2]. Drug therapy, encompassing a range of regimens such as blood pressure control, lipid regulation, plaque stabilization, and ventricular remodeling improvement, remains the primary treatment method for CVDs. Commonly used drugs include angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, β blockers, statins, and more. Although there has been significant progress in the understanding and treatment of CVDs over the past few decades, with a decrease in CVDs mortality in developed countries, the overall mortality rate in local areas and globally remains very high [3]. Furthermore, with an aging population, the challenge posed by CVDs will increase further, calling for new innovations in treatment.

For decades, due to their properties of low side effects and multiple therapeutic targets, herbal medicines have been used for the treatment and improvement of clinical symptoms in a wide range of diseases [4–7]. Therefore, traditional Chinese medicine and its components contribute to the treatment of heart failure. *Rosmarinus officinalis* L. belonging to the Lamiaceae family, is commonly known as rosemary and widely planted around the world. In traditional medicinal practices, rosemary has been employed to alleviate symptoms associated with kidney stones, menstrual discomfort, and muscular contractions. Modern medicine has shown that rosemary also has anti-fungal, antiviral, anti-infection, anti-inflammatory, anti-tumor, antithrombotic, anti-injury, antidepressant, anti-ulcer, antioxidant activities, and has been extensively explored in treating various ailments affecting the nervous, cardiovascular, digestive, urinary, endocrine, reproductive, respiratory, as well as dermatological systems [8, 9] (Figure 1). In some articles describing the pharmacological effects of rosemary, it is believed to have antihypertensive, anti-myocardial ischemia, anti-atherosclerosis, and heart failure improvement effects. Several experiments show that its efficacy is not weaker than current mainstream drugs, and it has fewer side effects, Although research articles focusing on the cardiovascular applications of rosemary constitute a relatively small fraction, approximately 3% of the total literature [9], its promising role in the prevention and management of CVDs has garnered significant attention. Therefore, it is necessary to systematically elaborate on the recent progress of rosemary in the cardiovascular field. This article summarizes the research progress and mechanisms of rosemary and its main active ingredients in CVDs such as hypertension, cardiac insufficiency, atherosclerosis, hyperlipidemia, and myocardial ischemia-reperfusion injury in recent years, providing new ideas for the treatment of CVDs with traditional herbal medicine.

Pharmacological properties of rosemary

Chemical components of rosemary

The chemical makeup of rosemary is primarily classified into two major categories: volatile components, also known as essential oils and non-volatile components. To date, a myriad of components including flavonoids, terpenes, diverse organic acids, branched-chain alkanes, and amino acids have been successfully isolated and identified. Terpenoids are the most abundant and complex compounds

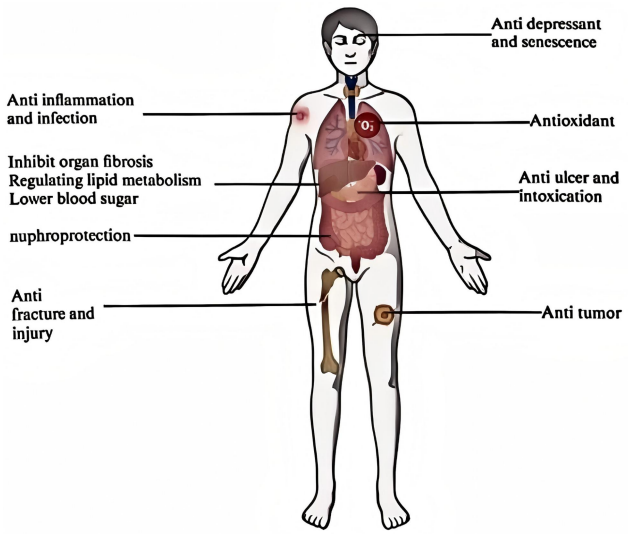


Figure 1 The application of rosemary in different systems other than cardiovascular system. The figure shows the pharmacological effects of rosemary on other systems besides cardiovascular system.

in rosemary. The essential oil derived from rosemary is primarily composed of monoterpenes and sesquiterpenes, which are its key constituents. At present, cineole, camphor, borneol, and other components have been isolated; The chemical composition analysis of phenolic compounds in rosemary extract shows that diterpenes are the main (multi) phenolic structures, accounting for 97.2% of the total phenolic content; The diterpenoid phenols in rosemary are the main antioxidant components, including rosmarinic acid (RA), oxalic acid, rosmarinol, salvianolic acid, etc. [9, 10]; In addition, terpenoid compounds also include triterpenoid components such as oleanolic acid, ursolic acid (UA), and betulinic acid. Carnosic acid (CA) stands as the most extensively researched bioactive compound, constituting approximately 30% of all studies, closely followed by carnosol, RA, and UA, which collectively make up another 35% of the research landscape. Figure 2 shows the chemical structural diagrams of these substances. Compared with the above compounds, there are relatively limited researches on substances such as betulinic acid, oleanolic acid, oligomers, and luteolin in CVDs. In the past two decades, researches on rosemary has mainly focused on its anti-cancer, antioxidant, antidepressant, and anti-infective effects [9]. However, RA from rosemary exhibits strong anti-cardiovascular disease effects. RA is prevalently found across diverse plant species, particularly those belonging to the Lamiaceae and Boraginaceae families, which include rosemary, sage, and bee balm, among others. Its presence has also been documented in plants from other families, such as the Umbelliferae and Cucurbitaceae [11, 12]. The chemical structure of RA is (2R)-2-[[(2"E")-3-(3,4-Dihydroxyphenyl)-1-oxo-2-propenyl] oxy]-3-(3,4-dihydroxyphenyl)propanoic acid, and its contents can serve as a valuable indicator for assessing the quality of herbal medications, providing a quantifiable metric for evaluating their purity and potency [13]. CA is also one of the main active substances in rosemary. Research indicates that CA and its derivatives account for over 90% of the antioxidant potency exhibited by rosemary acid extracts [14], and other effects include antibacterial [15], lipid metabolism regulation, and blood sugar reduction [16]. UA is also an important component of rosemary, with certain pharmacological activities in the treatment of CVDs. Modern pharmacology has demonstrated that rosemary extract has an extensive biological activities, including metabolism and blood pressure regulation, anti-neural injury, anti-inflammation, anti-aging, anti-cirrhosis, and anti-toxicity, in addition to the above-mentioned effects [9, 17].

Pharmacokinetics of rosemary

Absorption. Researches on the pharmacokinetics of rosemary extract primarily focus on RA, which can be administered through multiple routes, including oral, topical, ocular, pulmonary, and intravenous [18–21]. When administered orally, RA is primarily absorbed partially in the intestine via paracellular transport. Both experimental setups, in vivo (animal models) and in vitro (laboratory conditions), consistently reveal that the intestinal permeability of RA is rather low, with approximately 1% of the administered dose being absorbed in rats, underscoring its limited bioavailability through the gut. Factors such as food and acidic conditions in the digestive environment significantly affect RA absorption [22–24]. Generally, most phenolic compounds are difficult to absorb in the intestine. However, complex phenolic compounds can be broken down into simpler units (such as phenolic acids) by the action of intestinal flora [25]. RA can be degraded into two phenolic acids – m-coumaric and hydroxylated phenylpropionic acids – by intestinal flora, which can enhance absorption [26]. Ingesting RA in capsule form can reduce drug loss [27]. Although numerous studies focus on the topical application of RA [18], some literature suggests that RA can hardly penetrate the dermal layer in isolated skin. The application of natural penetrants, such as olive oil, may facilitate RA's penetration into deeper tissues [28].

The bioavailability of CA remains uncertain. After administering it orally to rats, Yan et al. reported a bioavailability of 65.09% [29], while Doolaege et al. reported a bioavailability of 40.1% at 6 h and speculated that the 24-h bioavailability could reach 97% [30]. As an antioxidant, CA exhibits extremely unstable chemical properties and can be rapidly oxidized to carnosol in the air [31]. When administered orally alone, CA is slowly absorbed by the intestine. Although CA can be detected in the body as early as 15 min after administration, it reaches its maximum concentration only after 120 min [29, 30]. When combined with other drugs, CA can rapidly achieve its maximum concentration (within 15 to 25 min), but the plasma concentration is significantly reduced, indicating that the absorption of CA is susceptible to other factors [32, 33].

UA is almost insoluble in water, with low dissolution and low oral bioavailability. After oral administration, UA is absorbed through passive diffusion, utilization of microemulsion-form UA could enhance its absorption rate [34]. Due to factors such as its low solubility and bioavailability, there are significant variations in the pharmacokinetic data of UA across different studies. For instance, Chen et al. showed that the $T_{1/2}$ after oral administration is less than 1 h, indicating that UA can be rapidly eliminated after oral intake [35]. Conversely, Liao et al. reported a $T_{1/2}$ of 4.3 h [36]. Synthetic UA analogues are believed to enhance drug efficacy and improve low utilization rates [37].

Distribution. RA in bloodstream could bind to plasma proteins and distribute through the circulatory system [38, 39]. Although various studies have been conducted, a deficiency in data persists regarding the distribution dynamics of RA throughout the human body. However, relevant data obtained from animal studies found that, in rats, local application of RA leads to distribution in the blood, skin, bones, and muscles; after intravenous application, the compound is also detected in the soft tissues of internal organs such as the spleen, liver, lungs, and heart [40]. Upon intraperitoneal administration in mice, the kidneys exhibit the highest concentration of RA, with the lungs, spleen, and liver following in descending order of abundance [13]. Some studies have pointed out that RA is difficult to penetrate the blood-brain barrier [13, 22]. Targeted drug delivery (such as intranasal) can not only increase the drug concentration in the brain but also reduce the metabolism of RA [41].

CA can be rapidly distributed throughout the body of rats. After intravenous administration, its $T_{1/2}$ (α) is only 0.8 min. After oral administration, substantial quantities of CA and its metabolic derivatives are present in the liver, intestine, and plasma. Its presence can also be detected in the brain. Currently, the pathway through which CA enters the brain remains unclear [30, 37].

UA has a wide tissue distribution. After rats were orally administered with 10 mg/kg UA for 1 h, the distribution pattern of UA

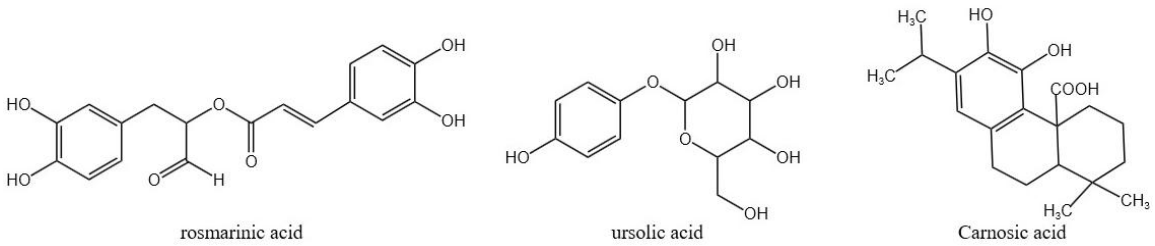


Figure 2 Chemical structure of three major compounds present in rosemary. The figure shows the chemical structures of rosmarinic acid, carnosic acid and ursolic acid.

concentration was observed as follows: lung > spleen > liver > brain > heart > kidney [35]. Given that UA is predominantly localized in tissues endowed with ample blood supply, this observation suggests a strong dependence of UA distribution on the blood flow and perfusion rates of various organs, underscoring the role of hemodynamic factors in its tissue distribution. However, some experiments also indicate that the distribution of UA has organ affinity. After oral administration, the concentration of UA in plasma is extremely low, and only after a sufficient period of feeding, the concentration of UA in plasma becomes significant [35, 42].

Metabolism. In the human body, glucuronidation is the primary metabolic pathway of RA, along with other metabolic pathways such as methylation and sulfation [43, 44]. Typically, the blood drug concentration reaches its peak 0.5–3 h after the administration of RA, and various metabolites such as caffeic acid, 2,4,5-trimethoxycinnamic acid, phenylacetic acid, protocatechuic acid, m-coumaric acid, p-hydroxybenzoic acid, vanillic acid, and ferulic acid are detected in the body [43, 45–47]. Different administration methods lead to variations in pharmacokinetics. By calculating the pharmacokinetics of RA using the pkCSM network tool, it can be inferred that its excretion rate is 0.25 mL/min/kg [48]. Although the main metabolites of RA are similar in rats and humans, there are significant differences in metabolic pathways and the number of metabolites. Therefore, it is necessary to conduct more human experiments [43, 49].

CA mainly exists in plasma in a free form. In rats fed with CA, the main metabolite of CA is glucoside derivatives, such as CA-glucoside, and other metabolites include methylated derivatives such as CA-12-methyl ether. The measurement of CA-glucoside concentration shows a “double peak”, which exhibits that there are peaks in liver and plasma concentrations at 50–100 min and about 800 min [32]. It is speculated that the appearance of the second peak may be attributed to enterohepatic circulation [50].

Currently, the metabolic pathways and processes surrounding UA remain largely unexplored, with a limited amount of research dedicated to clarifying its metabolic fate within the body. Existing reports indicate that UA is primarily metabolized in the liver. In vitro experiments reveal that UA can be metabolized by human liver microsomes containing the (reduced) nicotinamide adenine dinucleotide phosphate (NADPH) II generation system, achieving a conversion rate of approximately 40% within 20 min. However, it remains unmetabolized in samples lacking the NADPH generation system. The broad-spectrum inhibitor 1-aminobenzotriazole, which targets the cytochrome P450 enzyme system, can fully suppress the metabolism of UA in human liver microsomes. Inhibiting *CYP2C9, CYP3A4, CYP1A2, CYP2C8*, and *CYP2E1* can effectively hinder UA metabolism. Additionally, suppressing the expression of *CYP2A6, CYP2D6*, and *CYP2C19* also exerts a certain influence on UA metabolism, However, when 14 recombinant CYP subtypes were used for in vitro UA metabolism, it was found that only *CYP3A4* and *CYP2C9* could metabolize UA [34].

Excretion. RA is primarily excreted through the kidneys [51]. After taking 200 mg of RA to six volunteers, both RA and its metabolites were swiftly detected in both the plasma and urine. Upon measurement, it was found that the quantity of RA and its metabolic products eliminated via urine over 48 h accounted for 6.3 % of the total intake, with approximately 75% of this amount excreted within 6 h [43]. Given that the primary metabolic pathway of RA is glucuronidation, it’s possible that RA may also undergo metabolism through bile, as some RA metabolites have been identified in rat bile [40, 51]. In rats, CA is primarily eliminated via feces. Specifically, 32.2 ± 7.9% and 15.6 ± 8.2% of CA can be recovered in feces after intravenous and oral administration, respectively, suggesting that at least some CA is cleared from the liver in its native form [30]. Currently, research on the excretion of UA is limited. Animal experiments indicate that, aside from a very small amount excreted through the kidneys, most UA is metabolized and eliminated. Subsequent to intravenous administration, the hepatic concentration of UA undergoes a gradual yet steady rise, attaining its peak level at the 4-h mark. During this period, UA undergoes rapid elimination, indicating its active metabolism and clearance from the liver [34].

Safety. So far, most human experiments targeting RA have been conducted on a small number of subjects, and there is still a lack of randomized controlled trials using RA in a large population. No significant adverse reactions have been reported after using RA alone [21, 43, 45]. In some experiments using RA, subjects experienced headaches, constipation, diarrhea, worsening of cystic acne, and oily scalp, which often resolved on their own after discontinuing the medication [52]. There is still a lack of human experiments on CA, and Wang et al.’s determination of the toxicity of CA in rats showed an acute oral lethal dose (LD50) of 7,100 mg/kg, indicating its low toxicity characteristics [53]. As a drug that has been studied for a long time, many clinical experiments on UA have been conducted or are currently underway. In all experiments, UA has good oral tolerance and no statistically significant adverse reactions have occurred or been recorded [54–57]. In clinical trials, intravenous injection has good tolerance, and abdominal distension, nausea, diarrhea, and rash are the most reported adverse reactions. During the study, only a single participant encountered a grade 3 adverse event, characterized by the elevation of liver enzymes and the occurrence of diarrhea [58–60]. A study shows that UA has a certain degree of selective cytotoxicity, usually in pathological cells, which provides an advantage for UA as an anti-tumor drug [61].

Overall, the assessment of the safety of rosemary remains inadequate, with only a limited number of clinical trials having been or being conducted. More experiments are needed to evaluate the safety and potential risks of long-term use of rosemary. However, as a plant that has been long used in the production of herbal medicines, food, and cosmetics, its active ingredients are widely distributed in various other plants, and in many small sample clinical trials, it seems that no significant toxic side effects have been shown. Therefore, as a drug, rosemary may be considered relatively safe.

Table 1 [21, 26, 43, 45, 62, 63], Table 2 [29, 32, 33], and Table 3 [35, 36, 60] present the pharmacokinetic parameters of the three substances mentioned above in some studies.

The role of rosemary in the treatment of CVDs

Blood pressure regulation. RA controls blood pressure through various mechanisms. Alegría-Herrera et al. evaluated the antihypertensive effect of RA in a rat model, showing that the antihypertensive effect of RA is similar to that of telmisartan [64]. In rats with myocardial infarction (MI), After a four-week period of oral administration of RA, there was a notable decrease in ACE expression and a corresponding increase in ACE2 expression [65]. Further research indicates that RA exerts its antihypertensive effect by inhibiting the enzymatic activity of ACE. On one hand, it inhibits the activation of the RAAS system to reduce vasoconstriction. On the other hand, it activates the bradykinin system, increasing the release of vasodilator substances such as NO and prostaglandins [64, 66–68]. In isolated rat thoracic aorta, RA exhibited an endothelium-dependent vasodilatory effect [68]. Endothelin-1 (ET-1) can bind to vascular endothelial cells, induce the release of Ca^{2+} from the sarcoplasmic reticulum, and enhance the contraction of vascular smooth muscles. ET-1 can also mediate the production of reactive oxygen species (ROS) through NADPH oxidase, thereby inhibiting the efficacy of NO [69]. Research has shown that RA can inhibit the production of ET-1 in endothelial cells and the expression of the NADPH oxidase p22 phox subunit, exerting an endothelium-dependent antihypertensive effect [66]. RA can cause relaxation in rat endothelial-denuded aortic rings, suggesting that RA can also lower blood pressure in a non-endothelium-dependent manner. Wicha et al. confirmed that RA ethyl ester opens K^+ (Kv) channels and further hyperpolarizes membrane potential, thereby inhibiting voltage-operated calcium channels and receptor-operated calcium channels mediated Ca^{2+} influx. Additionally, inositol triphosphate-mediated sarcoplasmic reticulum Ca^{2+} release is also inhibited, through the aforementioned pathways, endothelial-independent antihypertensive effects are achieved [70].

Table 1 Pharmacokinetic parameters of rosmarinic acid in different experiments

Sample	The route of application	Drugs name	Dosages	Sample capacity	C_{max}	T_{max} (H)	$T_{1/2}$ (H)	CL (L/h/kg)	Reference
Human body	Intravenous	Mixtures containing ≥ 4.5% RA	100 mg	6 male and 6 female healthy volunteers	174.00 ng/mL	0.47	0.23	–	[43]
		Mixtures containing ≥ 4.5% RA	200 mg		308.00 ng/mL	0.54	0.58	–	
Human body	Peroral	*Perilla* extract containing 20% RA	200 mg	6 male healthy volunteers	1.20 μmol/L	0.50	–	–	[21]
Human body	Peroral	Plant extracts containing RA	RA 250 mg (fasted)	6 healthy volunteers	72.20 nmol/L	1.00	–	–	[45]
			RA 500 mg (fasted)		162.20 nmol/L	1.00	–	–	
			RA 500 mg (fed)		142.20 nmol/L	3.00	–	–	
Rat	Intravenous	*Salviae miltiorrhiza* extracts containing ≥10.1% RA	60 mg/kg	6 male rats	–	–	0.75	1.02	[62]
Rat	Gastric intubation	RA	100 umol/kg	3 male rats	1.36 μmol/L	0.17	0.95	–	[26]
Rat	Intravenous	*Salviae miltiorrhiza* extracts containing ≥3.92% RA	80 mg/kg	6 male rats	–	–	0.94	–	[63]
	Oral		800 mg/kg		1.86 μg/mL	0.17	1.06	–	

C_{max}, maximum serum concentration; T_{max}, time to reach the C_{max}; $T_{1/2}$, half-life period; CL, clearance (values of CL and C_{max} are the mean); RA, rosmarinic acid.

Table 2 Pharmacokinetic parameters of carnosic acid in different experiments

Sample	The route of application	Drugs name	Dosages	Sample capacity	C_{max}	T_{max} (H)	$T_{1/2}$ (H)	CL (L/min/kg)	Reference
Rat	Gastric intubation	*Rosmarinus officinalis* L. extract containing 38.9% CA	571 mg/kg	3 male rats	26.60 μmol/L	0.40	–	–	[32]
Rat	Gastric intubation	*Rosmarinus officinalis* L. extract containing 40% CA	100 mg/kg	6 male rats	54.02 μmol/L	0.25	3.50	–	[33]
Rat	Intravenous	*Rosmarinus officinalis* L. extract containing ≥ 98% CA	10 mg/kg	5 male rats	154.40 mg/L	–	1.13	0.003	[29]
	Gastric intubation		90 mg/kg	8 male rats	42.52 mg/L	2.09	16.03	0.003	

C_{max}, maximum serum concentration; T_{max}, time to reach the C_{max}; $T_{1/2}$, half-life period; CL, clearance (values of CL and Cmax are the mean); CA, carnosic acid.

Table 3 Pharmacokinetic parameters of ursolic acid in different experiments

Sample	The route of application	Drugs name	Dosages	Sample capacity	C_{max}	T_{max} (H)	$T_{1/2}$ (H)	CL	Reference
Human body	Intravenous	UA nanoliposomes containing 99.5% UA	37 mg/m^2	8 male healthy volunteers	1,835 ng/mL	4.03	4.59	8.67 L/h/m^2	[60]
		UA nanoliposomes containing 99.5% UA	74 mg/m^2		2,865 ng/mL	4.02	4.46	10.20 L/h/m^2	
		UA nanoliposomes containing 99.5% UA	98 mg/m^2		3,457 μmol/L	4.00	3.90	9.94 L/h/m^2	
Rat	Oral	UA	10 mg/kg	6 male rats	1.10 μg/mL	0.42	0.71	20.93 mL/h/mg	[35]
Rat	Gastric intubation	Lu-Ying Extract Containing UA 80.32 mg/kg	40 g/kg	6 male rats	294.8 ng/mL	1.00	4.30	1,130.1 mL/min/kg	[36]

C_{max}, maximum serum concentration; T_{max}, time to reach the C_{max}; $T_{1/2}$, half-life period; CL, clearance (values of CL and C_{max} are the mean); UA, ursolic acid.

RA also demonstrates selectivity in regulating blood pressure. Upon administration to both normotensive and hypertensive mice, RA was observed to selectively induce a decrease in systolic blood pressure solely among hypertensive rats, whereas it failed to exert any notable influence on the blood pressure levels of normotensive rats [67]. Another distinct clinical study, centered on patients diagnosed with primary hypotension, uncovered that the administration of rosemary essential oil was found to elicit a gradual and consistent elevation in blood pressure among the hypotensive patient population. This increase gradually stabilized and reverted to baseline levels upon discontinuation of the medication, without any alterations in heart rate observed throughout the duration of the study [71]. Overall, these experiments suggest that rosemary not only has significant effects on blood pressure control but also demonstrates unique safety profiles.

Many animal experiments have shown that UA possesses an endothelium-dependent vasodilatory function [72, 73]. As mentioned above, NO exerts a vasodilatory effect, whereas NADPH oxidase can inhibit its function. Specifically, factors like oxidative stress can stimulate the expression of endothelial nitric-oxide synthase (eNOS) in endothelial cells, thereby enhancing NO production and relaxing smooth muscles via the NO/cGMP pathway. Under the influence of endothelin, NADPH oxidase expression is upregulated. On the one hand, the produced superoxide elevates eNOS expression. On the other hand, superoxide promptly combines with NO to generate nitrite, which inactivates eNOS and ultimately results in the decoupling of NO and eNOS. UA increases eNOS production and phosphorylation by elevating p-AKT (protein kinase B) levels while reducing NADPH oxidase levels to lower blood pressure [74–77]. In stark contrast, a meticulous meta-analysis encompassing a broad spectrum of human studies failed to uncover any noteworthy influence of UA on either diastolic or systolic blood pressure [78].

Anti-myocardial hypoxia/reoxygenation (H/R). In the study of H9c2 cardiomyocyte apoptosis, RA inhibited the activation of transcription factor AP-1 by downregulating the expression of c-Jun N-terminal kinase and extracellular regulated protein kinase, thereby reducing the phosphorylation of *JUN-B, c-JUN, Fos*, and preventing the activation of downstream apoptotic genes, ultimately reducing cardiomyocyte apoptosis. Additionally, the study also found that RA has the effects of stabilizing mitochondrial membrane potential, regulating the expression of superoxide dismutase (SOD) and glutathione, and improving myocardial cell energy metabolism [79].

Myocardial injury often accompanies the accumulation of ROS, which can activate the expression of various substances such as Caspase-3 and nod-like receptor protein 3 (NLRP3), ultimately leading to apoptosis [80]. Nuclear factor erythroid-2 related factor 2 (Nrf2) can exert antioxidant effects by upregulating the expression of various substances. Previous studies have shown that Nrf2 can activate heme oxygenase-1 (*HO-1*) to inhibit oxidative stress-induced thermal degradation, thereby reducing renal ischemia-reperfusion injury [81]. CA enhances the expression of HO-1 by activating Nrf2, thereby antagonizing NLRP3-mediated apoptosis; CA also reduces oxidative stress by increasing SOD and glutathione peroxidase levels, and decreasing malondialdehyde and lipid ROS levels, thereby exerting cardioprotective effects [82].

Anti-myocardial ischemia/reperfusion injury. During MI, there is an increase in the ACE/ACE2 ratio and the expression of angiotensin 2. Angiotensin 2 can activate the AT1R/p38 MAPK (mitogen-activated protein kinase) pathway, leading to matrix fibrosis in cardiac cells and ultimately resulting in ventricular remodeling. After four weeks of treatment with RA in rats with MI, cardiac function improved and myocardial fibrosis was reduced. Research indicates that the use of RA can correct the alterations of ACE/ACE2 and angiotensin 2 in MI. During this process, both *AT1R* expression and phosphorylation of p38 MAPK are inhibited, suggesting that RA may exert its anti-myocardial infarction effect through this pathway [65]. The effectiveness of RA in combating ischemic reperfusion injury is intimately tied to its potent antioxidant properties. Molecular research conducted using AutoDock Vina software revealed that RA can closely binds to nuclear factor κB (NF-κB) p65, a key protein in the NF-κB pathway, inhibiting the activation and nuclear translocation of NF-κB, thereby reducing the key source of ROS in cells, the transcription and translation of ketoglutaric acid dehydrogenase, and ultimately alleviating myocardial ischemia-reperfusion injury [83].

In rat models, UA has been proved to reverse vascular cell ischemia in mice and improve heart failure in animals [72, 84]. Apoptosis, autophagy, and oxidative stress are involved in the process of myocardial ischemia-reperfusion injury. Radhiga et al.'s study showed that UA upregulates anti apoptotic molecules (such as Bcl-2 and Bcl xL) and downregulates proapoptotic proteins (including Bax caspase-3, -8, -9, Cytochrome c, TNF-α, and FAS) to inhibit apoptosis; By clearing superoxide radicals, the workload of SOD, catalase, glutathione peroxidase, glutathione-S-transferase, and glutathione reductase is reduced; Exert anti fibrotic effects by downregulating the expression of matrix metalloproteinases (MMP-2, MMP-9), type I collagen, alpha smooth muscle actin, and transforming growth factor-β (TGF-β) [85, 86]. Senthil et al. pointed out that UA can reduce the activity of myeloperoxidase and inhibit the infiltration of neutrophils into damaged myocardium; in addition, UA also has a membrane stabilizing effect [87]. Nonetheless, certain experimental findings indicate that UA may exacerbate myocardial tissue injury by fostering the infiltration of inflammatory cells at the infarct site [86]. Therefore, further research is still needed.

Following ischemia/reperfusion injury, various arrhythmias often occur. Although Somova et al.'s experiment did not reveal that UA could decrease the incidence of arrhythmias in rats post-ischemic treatment, UA demonstrated remarkable antiarrhythmic effects in mice with arrhythmias induced by calcium chloride and adrenaline, comparable to amiodarone and propranolol, respectively. This could potentially offer a novel strategy for antiarrhythmic therapy [72].

In the isoproterenol induced myocardial stress model in mice, CA preconditioning attenuated the increases in serum troponin I, CK-MB, lactate dehydrogenase, and transaminase levels, as well as the pathological changes in cardiac tissue. In the myocardium, CA treatment inhibited the expression of apoptosis proteins Bax, caspase-3, caspase-9, and p53, and restored the activity of Bcl-2. In addition, the activation of Nrf2 and HO-1 was detected [88]. The aforementioned experiments underscore the pivotal function of the Nrf2 and HO-1 signaling cascades in mediating the cardioprotective effects of CA, a finding that has been corroborated in vitro as well [82].

Supplementation of rosemary after MI in rats improved diastolic function, left ventricular hypertrophy, and left ventricular diameter; In addition, the damaged myocardium exhibited an energy metabolism similar to that of a normal heart, demonstrating the protective effect of rosemary leaves on the heart [89]. However, in this experiment, the expression of Nrf2 and HO-1 was not affected, which is different from previous studies [82, 88]. Interestingly, rosemary also showed an antiplatelet effect in rats, which may help prevent MI [7].

Improve cardiac function. In eukaryotes, the universally preserved serine/threonine protein kinase known as adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) holds a paramount position as a sentinel of cellular energy status, intricately orchestrating the maintenance of energy equilibrium within cells through its regulatory mechanisms. Smad3 is one of the key transcription factors mediating the pathogenesis of cardiac fibrosis, and targeting *Smad3* can inhibit the occurrence and progression of cardiac fibrosis [90]. Research by Zhang X and others has shown that in mice with long-term pressure overload, RA, with the help of the nuclear receptor PPAR-γ, activates AMPK to inhibit the phosphorylation and nuclear translocation of *Smad3*, thereby alleviates myocardial fibrosis and improves cardiac function [91], however ventricular hypertrophy was not improved in this process. Studies on the anti-fibrotic effect of RA on liver cells also found an increase in PPARγ levels [92]. Similarly, research by Joardar S has confirmed that the AMPK-Smad3 pathway plays an important role in RA's anti-fibrotic effects, however, the results of this experiment

showed that PPAR-γ was not involved in this process [93]. The *MAPK* and AKT signaling pathways are crucial regulators of cardiac hypertrophy and fibrosis. They mediate various cellular processes involved in the development and progression of these pathological conditions. Studies have shown that RA can regulate their activity [65, 79, 94], suggesting that RA can improve cardiac function through multiple pathways. In fructose-fed hypertensive rats, RA exerts cardioprotective and antihypertensive effects by inhibiting the expression of the NADPH oxidase p22phox subunit. But the mechanism remains unclear [66]. RA also exhibits a beneficial impact on diabetic cardiomyopathy (DCM). Research by Diao J has shown that RA activates the *SIRT 1/PGC-1α* pathway (regulators of sugar and lipid metabolism), stabilizing mitochondrial membrane potential and inhibiting cell apoptosis, thereby improving cardiac function and mitochondrial damage in DCM mice [95].

Heat stress can induce cardiac dysfunction and lead to death, and the activation of the PERK/eIF2α/CHOP unfolded protein response mediates cell apoptosis. UA can inhibit the activation of CHOP protein at the transcriptional level. At the same time, UA induces the expression of anti-apoptotic protein Mcl-1, thereby suppressing the expression of CHOP downstream protein Puma, ultimately inhibiting cardiomyocyte apoptosis. In a heat shock mouse model, mice pretreated with UA for two days showed significantly improved survival rates compared to the control group [96]. Doxorubicin, a widely utilized anthracycline chemotherapeutic agent, is notorious for its adverse effect of triggering cardiomyocyte apoptosis via the activation of ROS. UA improved the left ventricular fractional shortening and left ventricular ejection fraction in doxorubicin-treated mice, the mechanism is similar to the above-mentioned increase in eNOS expression and decrease in NADPH (NOX4) oxidase [77], a major source of ROS [74, 97]. In DCM rats, the administration of UA directly and indirectly reduced the expression of the pro-fibrotic factor TGF-β1, suggesting that UA has anti-fibrotic potential [98]. UA also has an anti-pulmonary arterial hypertension effect. After 4 weeks of treatment with UA in monocrotaline-induced PAH rats, myocardial hypertrophy and fibrosis improved, and right ventricular hemodynamic parameters were improved. Proteomic analysis indicated that UA potentially altered lipid metabolism in pulmonary arterial hypertension mice. Subsequent research demonstrated that UA notably boosted the expression of lipid metabolism genes, namely *PPARα* and *CPT1b*. Additionally, *PPARα* agonist fenofibrate has been shown to reduce ventricular hypertrophy, implying that UA might hinder ventricular remodeling through lipid metabolism regulation [99].

Cardiac remodeling, intricately linked to oxidative stress, disrupts the heart's normal pumping function, progressively impairing its ability to effectively circulate blood and ultimately predisposing individuals to heart failure [100]. Studies have shown that Nox2 can induce ROS production in rats, promote myocardial cell hypertrophy, and lead to cardiac fibrosis [101, 102]. Activated AKT stimulates downstream GSK3β, which also participates in the pathophysiology of cardiac hypertrophy [103, 104]. Investigations conducted on murine models of ventricular remodeling induced by pressure overload have revealed that CA exerts a protective effect by mitigating cardiac hypertrophy, fibrosis, oxidative stress, and apoptotic cell death through the inhibition of the AKT/GSK3β/NOX4 signaling cascade [105].

Anti-atherosclerosis. RA has the effects of regulating blood lipids and anti-atherosclerosis. In experiments on mice, the levels of TNF-α, IL-1β, and CRP in RA-fed mice decreased, and the plaque area and arterial stenosis also improved, showing similar effects to atorvastatin [106]. The onset of atherosclerosis is often regarded as initiating with endothelial damage, which marks the initial stage in its developmental cascade [107]. RA can potently suppress the triggering of the NLRP3 inflammasome and the subsequent development of endothelial dysfunction, achieved by modulating the downregulation of the p38-foxO1-TXNIP signaling axis [108]. The transformation of macrophages into foam cells represents a crucial milestone in the advancement of atherosclerosis. RA can differentially regulate the expression of ATP-binding cassette transporter A1 through JAK 2/STAT 3, c-Jun N-terminal kinase, and PKC-p38, and reduce the degradation of ATP-binding cassette transporter A1, thereby promoting macrophage cholesterol efflux and hindering the progression of atherosclerosis [109]. Diabetes and obesity also figure prominently among the various risk factors that contribute to the development of atherosclerosis. In hyperlipidemic *C57BL/6J* mice induced by a high-fat diet, RA augmented the expression of hepatic receptors involved in cholesterol uptake, specifically scavenger receptor class B type 1 and low-density lipoprotein receptor, while concurrently upregulating the expression of cholesterol efflux-mediating molecules such as ATP-binding cassette transporters G5 and G8, as well as cholesterol 7α-hydroxylase A1. And it also promoted fatty acid β-oxidation through AMPK-mediated carnitine palmitoyltransferase 1A induction, thereby promoting cholesterol uptake, efflux, and fatty acid oxidation, reducing the body weight, blood glucose, plasma, and liver cholesterol and triglycerides in mice. During this process, RA also showed a better cholesterol efflux capacity than metformin [110]. Adiponectin is a lipid factor produced and secreted by adipocytes, playing an important role in lipid reduction, anti-atherosclerosis, and enhancing insulin sensitivity [111], its level increases during adipocyte differentiation [112]. Research has demonstrated that RA exerts a down-regulatory effect on the expression of transcription factors C/EBPα and PPARγ, thereby reducing adiponectin levels through post-transcriptional regulation and inhibiting the formation of adipocytes. This process involves the engagement of both TGF-β and IL-17A. Although the regulatory effect of RA on PPARγ is inconsistent with that observed in hypertension studies, there is no doubt that RA's regulation of body weight makes it a potential new weight loss drug [113].

The influence of UA on atherosclerosis has been a subject of ongoing debate and remains inconclusive. In mice administered with UA, a reduction in plaque area was observed, and UA was more effective than resveratrol in reducing plaques [114–116]. The MAPK pathway can stimulate the adhesion and chemotactic activity of monocytes, monocytes release inflammatory factors and ROS, which can lead to inflammation and fibrosis of the vascular wall, promoting the progression of atherosclerosis. MAPK phosphatase 1 can inversely regulate the MAPK pathway. In $LDLR^{-/-}$ mice administered with a high-fat diet, UA has been observed to mitigate atherosclerotic plaque formation by safeguarding MAPK phosphatase 1 against oxidative degradation, thereby exerting a protective effect. Experiments in cell culture have shown that UA increases the mRNA expression of autophagy-related proteins (Atg 5 and Atg 1611), promoting autophagy in macrophages; Furthermore, UA enhances the efflux of cholesterol from macrophages loaded with low-density lipoprotein towards apolipoprotein A-1 [116]. Research on rat primary cultured smooth muscle cells reveals that UA exerts a significant anti-proliferative effect by inhibiting the expression of *miRNA-21* and enhancing the expression of the tumor suppressor gene *PTEN* [117]. Numerous studies have demonstrated that UA, acting through multiple pathways, such as inhibiting the degradation of IκBs (inhibitors of κB) by TNF-α and suppressing ROS production, effectively blocks NF-κB activity. This results in a reduction of adhesion molecules, including VCAM-1, ICAM-1, and E-selectin, which facilitate the aggregation of inflammatory cells during the early stages of atherosclerosis. Simultaneously, the expression of proteins that promote inflammatory cell aggregation and vascular smooth muscle cell migration, such as MMP-2, also decreases. Ultimately, this slows down the progression of atherosclerosis [116, 118–121]. Furthermore, RA can inhibit cholesterol ester transfer protein mediated cholesterol ester transfer (HDL-C to VLDL) [122, 123]. The above studies suggest that UA has anti-atherosclerotic effects, yet no changes in blood lipids were observed in previous studies [114–116, 124]. Messner's research showed that supplementation with UA in mice resulted in a marked augmentation of atherosclerotic plaques, with the extent of this increase being directly proportional to the administered dose; for human umbilical vein endothelial cells, UA induces apoptosis [124]. Research by Hua et al. also showed that UA

reduces the uptake of rosuvastatin by inhibiting the OATP1B1 transporter [125]. Indeed, given the promising findings regarding the anti-atherosclerotic effects of UA, conducting further research is imperative to comprehensively evaluate its efficacy and potential clinical applications. This could involve studying its mechanisms of action in more detail, assessing its safety and tolerability in various populations, and determining optimal dosing strategies.

CA regulates atherosclerosis through multiple pathways. CA can inhibit the activity of gastric lipase [126], and regulate the gut microbiota, increasing fecal excretion, thereby reducing body weight in mice and rats without altering food intake [126, 127]. In vitro experiments have shown that the fat production in preadipocytes treated with CA is suppressed, which may be related to the suppression of the expression of key transcription factors C/EBPa and PPARγ involved in fat production [128], this effect has been confirmed in mice, mediated by the EGFR/MAPK pathway [129]. Research by Liao et al. indicates that CA exerts anti-adipogenic effects in liver tissues of mice treated with bisphenol A by reducing adipogenic proteins FAS and aP2 and increasing lipolytic protein adipose triacylglyceride lipase, possibly through the SIRT1/FoxO1 pathway [130]. All these experiments observed a decrease in blood lipid levels. However, reports of CA directly acting on atherosclerosis are limited, and there is a lack of comparison with traditional lipid-lowering drugs. In the limited data, CA appears to demonstrate stronger weight loss effects rather than anti-atherosclerosis effects. Therefore, more experiments are needed to understand the characteristics of this substance.

The anti-atherosclerosis effect of rosemary has been widely reported [16, 131–135]. In rats treated with rosemary, rosemary extract reduced total cholesterol, phospholipids, triglycerides, and the atherosclerosis index. Its lipid-lowering effect may be related to promoting insulin secretion and inhibiting the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase [133]. Reports indicate that rosemary extract can regulate lipid metabolism by inhibiting the activity of sterol-regulatory element binding proteins (SREBPs) [16]. The mechanism has been further elucidated in the extract of *Melissa officinalis* containing RA. Studies have shown that the *Melissa officinalis* extract reduces blood lipids by inhibiting the expression of *SREBP-1c* and response genes in fatty acid synthesis (including *FAS, SCD1*, and *ACC1*), reducing the nuclear abundance of the key transcription factor SREBP-2 for liver cholesterol synthesis, and inducing bile acid synthesis [134].

In addition, since RA, UA, and CA are all effective components of rosemary, the pathways involved in the above studies, such as AMPK and PPARγ, may also mediate the anti-atherosclerosis effect of rosemary [134, 135].

Discussion and conclusion

In recent years, commonly used cardiovascular drugs gradually can not meet people's needs, and natural ingredients in plants have attracted much attention due to their low side effects and stability. As a traditional herb, rosemary was considered to have the effects of sweating, strengthening the spleen, calming the nerves, and relieving pain in ancient times. In the past 20 years, the number of studies on rosemary has increased significantly. A large number of studies have shown that rosemary has unique pharmacological effects, especially in the field of cardiovascular health. Currently, there are some articles summarizing the pharmacological effects of rosemary and its components, with most of them mentioning the therapeutic effects of rosemary on heart disease. Nevertheless, a systematic review specifically addressing the application of rosemary in the cardiovascular field is still lacking. This paper summarizes the pharmacokinetic characteristics of the main components of rosemary and their pharmacological effects in the treatment of CVDs for the first time, elucidating its mechanism in addressing a range of conditions including hypertension, myocardial ischemia, cardiac insufficiency, and atherosclerosis. It highlights its efficacy in managing diverse conditions including hypertension, myocardial ischemia, cardiac insufficiency, and atherosclerosis. Specifically, rosemary primarily lowers blood pressure by inhibiting the RAAS system and vascular endothelium. It enhances cardiac function via antioxidant activity, suppression of apoptosis, and inhibition of myocardial fibrosis. Additionally, it combats atherosclerosis through multiple mechanisms, including promoting fat excretion, augmenting liver uptake, preventing fat deposition in blood vessels, and bolstering fat oxidation. In numerous studies, rosemary has demonstrated efficacy comparable to existing medications, highlighting its potential as a viable substitute or complement to current therapeutic agents. Nevertheless, several limitations persist. The majority of current experiments are conducted on animals, with a notable absence of long-term human trials involving large populations. This absence hinders thorough evaluation of rosemary's safety and potential adverse effects, and the drug's interactions with various medications remain unclear. Further investigation into this promising drug could yield significant benefits for clinical practice.

References

1. GBD 2017 Mortality Collaborators. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1684–1735. Available at: http://doi.org/10.1016/s0140-6736(18)31891-9
2. Rosengren A, Hawken S, Ôunpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):953–962. Available at: http://doi.org/10.1016/S0140-6736(04)17019-0
3. Li Y, Cao GY, Jing WZ, Liu J, Liu M. Global trends and regional differences in incidence and mortality of cardiovascular disease, 1990–2019: findings from 2019 global burden of disease study. *Eur J Prev Cardiol.* 2023;30(3):276–286. Available at: http://doi.org/10.1093/eurjpc/zwac285
4. Palombo EA. Traditional Medicinal Plant Extracts and Natural Products with Activity against Oral Bacteria: Potential Application in the Prevention and Treatment of Oral Diseases. *Evid Based Complement Alternat Med.* 2011;201:680354. Available at: http://doi.org/10.1093/ecam/nep067
5. Pazyar N, Yaghoobi R, Rafiee E, Mehrabian A, Feily A. Skin Skin wound healing and phytomedicine: a review. *Skin Pharmacol Physiol.* 2014;27(6):303–310. Available at: http://doi.org/10.1159/000357477
6. Pérez-Sánchez A, Barrajón-Catalán E, Caturla N, et al. Protective effects of citrus and rosemary extracts on UV-induced damage in skin cell model and human volunteers. *J Photochem Photobiol B.* 2014;136:12–18. Available at: http://doi.org/10.1016/j.jphotobiol.2014.04.007
7. Yimam M, Lee YC, Jiao P, Hong M, Brownell L, Jia Q. A Standardized Composition Comprised of Extracts from Rosmarinus officinalis, Annona squamosa and Zanthoxylum clava-herculis for Cellulite. *Pharmacognosy Res.* 2017;9(4):319–324. Available at: http://doi.org/10.4103/pr.pr_70_17
8. Ojeda-Sana AM, van Baren CM, Elechosa MA, Juárez MA, Moreno S. New insights into antibacterial and antioxidant activities of rosemary essential oils and their main components. *Food Control.* 2013;31(1):189–195. Available at: http://doi.org/10.1016/j.foodcont.2012.09.022
9. Andrade JM, Faustino C, Garcia C, Ladeiras D, Reis CP, Rijo P. Rosmarinus officinalis L.: an update review of its phytochemistry and biological activity. *Future Sci.* 2018;4(4):FSO283. Available at: http://doi.org/10.4155/fsoa-2017-0124
10. Mena P, Cirlini M, Tassotti M, Herrlinger KA, Dall'Asta C, Del

Rio D. Phytochemical Profiling of Flavonoids, Phenolic Acids, Terpenoids, and Volatile Fraction of a Rosemary (Rosmarinus officinalis L.) Extract. *Molecules.* 2016;21(11):1576. Available at: http://doi.org/10.3390/molecules21111576
11. Petersen M, Abdullah Y, Benner J, et al. Evolution of rosmarinic acid biosynthesis. *Phytochemistry.* 2009;70(15–16):1663–1679. Available at: http://doi.org/10.1016/j.phytochem.2009.05.010
12. Petersen M, Simmonds MS. Rosmarinic acid. *Phytochemistry.* 2003;62(2):121–125. Available at: http://doi.org/10.1016/s0031-9422(02)00513-7
13. Hitl M, Kladar N, Gavarić N, Božin B. Rosmarinic Acid-Human Pharmacokinetics and Health Benefits. *Planta Med.* 2021;87(4):273–282. Available at: http://doi.org/10.1055/a-1301-8648
14. Aruoma OI, Halliwell B, Aeschbach R, Löligers J. Antioxidant and pro-oxidant properties of active rosemary constituents: carnosol and carnosic acid. *Xenobiotica.* 1992;22(2):257–268. Available at: http://doi.org/10.3109/00498259209046624
15. Del Campo J, Amiot MJ, Nguyen-The C. Antimicrobial effect of rosemary extracts. *J Food Prot.* 2000;63(10):1359–1368. Available at: http://doi.org/10.4315/0362-028X-63.10.1359
16. Xie ZS, Zhong LJ, Wan XM, et al. Petroleum ether sub-fraction of rosemary extract improves hyperlipidemia and insulin resistance by inhibiting SREBPs. *Chin J Nat Med.* 2016;14(10):746–756. Available at: http://doi.org/10.1016/S1875-5364(16)30089-9
17. Alavi MS, Fanoudi S, Ghasemzadeh Rahbardar M, Mehri S, Hosseinzadeh H. An updated review of protective effects of rosemary and its active constituents against natural and chemical toxicities. *Phytother Res.* 2021;35(3):1313–1328. Available at: http://doi.org/10.1002/ptr.6894
18. de Macedo LM, Santos ÉMD, Militão L, et al. Rosemary (Rosmarinus officinalis L., syn Salvia rosmarinus Spenn.) and Its Topical Applications: A Review. *Plants (Basel).* 2020;9(5):651. Available at: http://doi.org/10.3390/plants9050651
19. Carović-StanKo K, PeteK M, Grdiša M, et al. Medicinal plants of the family Lamiaceae as functional foods – a review. *Czech J Food Sci.* 2016;34(5):377–390. Available at: http://doi.org/10.17221/504/2015-CJFS
20. Lu P, Xing Y, Xue Z, et al. Pharmacokinetics of salvianolic acid B, rosmarinic acid and Danshensu in rat after pulmonary administration of Salvia miltiorrhiza polyphenolic acid solution. *Biomed Chromatogr.* 2019;33(8):e4561. Available at: http://doi.org/10.1002/bmc.4561
21. Jia JY, Lu YL, Li XC, et al. 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(4):260–271. Available at: http://doi.org/10.1016/j.curtheres.2010.08.004
22. Hase T, Shishido S, Yamamoto S, et al. Rosmarinic acid suppresses Alzheimer's disease development by reducing amyloid β aggregation by increasing monoamine secretion. *Sci Rep.* 2019;9(1):8711. Available at: http://doi.org/10.1038/s41598-019-45168-1
23. 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(12):4740–4746. Available at: http://doi.org/10.1021/jf0478307
24. Domínguez-Avila JA, Wall-Medrano A, Velderrain-Rodríguez GR, et al. Gastrointestinal interactions, absorption, splanchnic metabolism and pharmacokinetics of orally ingested phenolic compounds. *Food Funct.* 2017;8(1):15–38. Available at: http://doi.org/10.1039/c6fo01475e
25. Velderrain-Rodríguez GR, Palafox-Carlos H, Wall-Medrano A, et al. Phenolic compounds: their journey after intake. *Food Funct.* 2014;5(2):189–197. Available at: http://doi.org/10.1039/C3FO60361J
26. Konishi Y, Kobayashi S. Transepithelial transport of rosmarinic acid in intestinal Caco-2 cell monolayers. *Biosci Biotechnol Biochem.* 2005;69(3):583–591. Available at: http://doi.org/10.1271/bbb.69.583
27. de Torre MP, Vizmanos JL, Cavero RY, Calvo MI. Improvement of antioxidant activity of oregano (Origanum vulgare L.) with an oral pharmaceutical form. *Biomed Pharmacother.* 2020;129:110424. Available at: http://doi.org/10.1016/j.biopha.2020.110424
28. Stelmakienė A, Ramanauskienė K, Briedis V. Release of rosmarinic acid from semisolid formulations and its penetration through human skin ex vivo. *Acta Pharm.* 2015;65(2):199–205. Available at: http://doi.org/10.1515/acph-2015-0012
29. Yan H, Wang L, Li X, et al. High-performance liquid chromatography method for determination of carnosic acid in rat plasma and its application to pharmacokinetic study. *Biomed Chromatogr.* 2009;23(7):776–781. Available at: http://doi.org/10.1002/bmc.1184
30. Doolaege EH, Raes K, De Vos F, Verhé R, De Smet S. Absorption, distribution and elimination of carnosic acid, a natural antioxidant from Rosmarinus officinalis, in rats. *Plant Foods Hum Nutr.* 2011;66(2):196–202. Available at: http://doi.org/10.1007/s11130-011-0233-5
31. Schwarz K, Ternes W. Antioxidative constituents of Rosmarinus officinalis and Salvia officinalis. *Z Lebensm Unters Forch.* 1992;195(2):95–98. Available at: http://doi.org/10.1007/BF01201765
32. Romo Vaquero M, García Villalba R, Larrosa M, et al. Bioavailability of the major bioactive diterpenoids in a rosemary extract: metabolic profile in the intestine, liver, plasma, and brain of Zucker rats. *Mol Nutr Food Res.* 2013;57(10):1834–1846. Available at: http://doi.org/10.1002/mnfr.201300052
33. Veenstra JP, Vemu B, Tocmo R, Nauman MC, Johnson JJ. Pharmacokinetic Analysis of Carnosic Acid and Carnosol in Standardized Rosemary Extract and the Effect on the Disease Activity Index of DSS-Induced Colitis. *Nutrients.* 2021;13(3):773. Available at: http://doi.org/10.3390/nu13030773
34. Jinhua W. Ursolic acid: Pharmacokinetics process in vitro and in vivo, a mini review. *Arch Pharm (Weinheim).* 2019;352(3):e1800222. Available at: http://doi.org/10.1002/ardp.201800222
35. Chen Q, Luo S, Zhang Y, Chen Z. Development of a liquid chromatography–mass spectrometry method for the determination of ursolic acid in rat plasma and tissue: Application to the pharmacokinetic and tissue distribution study. *Anal Bioanal Chem.* 2011;399(8):2877–2884. Available at: http://doi.org/10.1007/s00216-011-4651-x
36. Liao Q, Yang W, Jia Y, Chen X, Gao Q, Bi K. LC-MS determination and pharmacokinetic studies of ursolic acid in rat plasma after administration of the traditional chinese medicinal preparation Lu-Ying extract. *Yakugaku Zasshi.* 2005;125(6):509–515. Available at: http://doi.org/10.1248/yakushi.125.509
37. Erdmann J, Kujaciński M, Wiciński M. Beneficial Effects of Ursolic Acid and Its Derivatives – Focus on Potential Biochemical Mechanisms in Cardiovascular Conditions. *Nutrients.* 2021;13(11):3900. Available at: http://doi.org/10.3390/nu13113900
38. Peng X, Wang X, Qi W, Su R, He Z. Affinity of rosmarinic acid to human serum albumin and its effect on protein conformation

stability. *Food Chem.* 2016;192:178–187. Available at: http://doi.org/10.1016/j.foodchem.2015.06.109
39. Shamsi A, Ahmed A, Khan MS, Al Shahwan M, Husain FM, Bano B. Understanding the binding between Rosmarinic acid and serum albumin: In vitro and in silico insight. *J Mol Liq.* 2020;311:113348. Available at: http://doi.org/10.1016/j.molliq.2020.113348
40. Nunes S, Madureira AR, Campos D, et al. Therapeutic and nutraceutical potential of rosmarinic acid-Cytoprotective properties and pharmacokinetic profile. *Crit Rev Food Sci Nutr.* 2017;57(9):1799–1806. Available at: http://doi.org/10.1080/10408398.2015.1006768
41. Bhatt R, Singh D, Prakash A, Mishra N. Development, characterization and nasal delivery of rosmarinic acid-loaded solid lipid nanoparticles for the effective management of Huntington's disease. *Drug Deliv.* 2015;22(7):931–939. Available at: http://doi.org/10.3109/10717544.2014.880860
42. Yin MC, Lin MC, Mong MC, Lin CY. Bioavailability, distribution, and antioxidative effects of selected triterpenes in mice. *J Agric Food Chem.* 2012;60(31):7697–7701. Available at: http://doi.org/10.1021/jf302529x
43. Baba S, Osakabe N, Natsume M, et al. Absorption, metabolism, degradation and urinary excretion of rosmarinic acid after intake of Perilla frutescens extract in humans. *Eur J Nutr.* 2005;44:1–9. Available at: http://doi.org/10.1007/s00394-004-0482-2
44. Su J, Jia F, Lu J, et al. Characterization of the metabolites of rosmarinic acid in human liver microsomes using liquid chromatography combined with electrospray ionization tandem mass spectrometry. *Biomed Chromatogr.* 2020;34(4):e4806. Available at: http://doi.org/10.1002/bmc.4806
45. Noguchi-Shinohara M, Ono K, Hamaguchi T, et al. Pharmacokinetics, Safety and Tolerability of Melissa officinalis Extract which Contained Rosmarinic Acid in Healthy Individuals: A Randomized Controlled Trial. *PLoS One.* 2015;10(5):e0126422. Available at: http://doi.org/10.1371/journal.pone.0126422
46. Mosele JI, Martín-Peláez S, Macià A, et al. Study of the catabolism of thyme phenols combining in vitro fermentation and human intervention. *J Agric Food Chem.* 2014;62(45):10954–10961. Available at: http://doi.org/10.1021/jf503748y
47. Nurmi A, Nurmi T, Mursu J, Hiltunen R, Voutilainen S. Ingestion of oregano extract increases excretion of urinary phenolic metabolites in humans. *J Agric Food Chem.* 2006;54(18):6916–6923. Available at: http://doi.org/10.1021/jf060879n
48. Noor S, Mohammad T, Rub MA, et al. Biomedical features and therapeutic potential of rosmarinic acid. *Arch Pharm Res.* 2022;45(4):205–228. Available at: http://doi.org/10.1007/s12272-022-01378-2
49. Nakazawa T, Ohsawa K. Metabolism of rosmarinic acid in rats. *J Nat Prod.* 1998;61(8):993–996. Available at: http://doi.org/10.1021/np980072s
50. Ma Y, Li P, Chen D, Fang T, Li H, Su W. LC/MS/MS quantitation assay for pharmacokinetics of naringenin and double peaks phenomenon in rats plasma. *Int J Pharm.* 2006;307(2):292–299. Available at: http://doi.org/10.1016/j.ijpharm.2005.10.018
51. Zhang J, Wen Q, Qian K, Feng Y, Luo Y, Tan T. Metabolic profile of rosmarinic acid from Java tea (Orthosiphon stamineus) by ultra-high-performance liquid chromatography coupled to quadrupole-time-of-flight tandem mass spectrometry with a three-step data mining strategy. *Biomed Chromatogr.* 2019;33(9):e4599. Available at: http://doi.org/10.1002/bmc.4599
52. Connelly AE, Tucker AJ, Tulk H, et al. High-rosmarinic acid spearmint tea in the management of knee osteoarthritis symptoms. *J Med Food.* 2014;17(12):1361–1367. Available at: http://doi.org/10.1089/jmf.2013.0189
53. Wang QL, Li H, Li XX, et al. Acute and 30-day oral toxicity studies of administered carnosic acid. *Food Chem Toxicol.* 2012;50(12):4348–4355. Available at: http://doi.org/10.1016/j.fct.2012.08.057
54. Cione JGC, Verlengia R, Barbosa CGR, et al. No additional effects of ursolic acid supplementation associated with combined exercise program on metabolic syndrome of postmenopausal women: A double-blind, randomized, placebo-controlled trial. *Clin Nutr ESPEN.* 2021;44:143–149. Available at: http://doi.org/10.1016/j.clnesp.2021.05.031
55. Church DD, Schwarz NA, Spillane MB, et al. l-Leucine Increases Skeletal Muscle IGF-1 but Does Not Differentially Increase Akt/mTORC1 Signaling and Serum IGF-1 Compared to Ursolic Acid in Response to Resistance Exercise in Resistance-Trained Men. *J Am Coll Nutr.* 2016;35(7):627–638. Available at: http://doi.org/10.1080/07315724.2015.1132019
56. Lobo PCB, Vieira IP, Pichard C, et al. Ursolic acid has no additional effect on muscle strength and mass in active men undergoing a high-protein diet and resistance training: A double-blind and placebo-controlled trial. *Clin Nutr.* 2021;40(2):581–589. Available at: http://doi.org/10.1016/j.clnu.2020.06.004
57. Ramírez-Rodríguez AM, González-Ortiz M, Martínez-Abundis E, Acuña Ortega N. Effect of Ursolic Acid on Metabolic Syndrome, Insulin Sensitivity, and Inflammation. *J Med Food.* 2017;20(9):882–886. Available at: http://doi.org/10.1089/jmf.2017.0003
58. Wang XH, Zhou SY, Qian ZZ, et al. Evaluation of toxicity and single-dose pharmacokinetics of intravenous ursolic acid liposomes in healthy adult volunteers and patients with advanced solid tumors. *Expert Opin Drug Metab Toxicol.* 2013;9(2):117–125. Available at: http://doi.org/10.1517/17425255.2013.738667
59. Zhu Z, Qian Z, Yan Z, Zhao C, Wang H, Ying G. A phase I pharmacokinetic study of ursolic acid nanoliposomes in healthy volunteers and patients with advanced solid tumors. *Int J Nanomedicine.* 2013;8:129–136. Available at: http://doi.org/10.2147/IJN.S38271
60. Qian Z, Wang X, Song Z, et al. A phase I trial to evaluate the multiple-dose safety and antitumor activity of ursolic acid liposomes in subjects with advanced solid tumors. *Biomed Res Int.* 2015;2015:809714. Available at: http://doi.org/10.1155/2015/809714
61. Kashyap D, Tuli HS, Sharma AK. Ursolic acid (UA): A metabolite with promising therapeutic potential. *Life Sci.* 2016;146:201–213. Available at: http://doi.org/10.1016/j.lfs.2016.01.017
62. Li X, Yu C, Lu Y, et al. Pharmacokinetics, tissue distribution, metabolism, and excretion of depside salts from Salvia miltiorrhiza in rats. *Drug Metab Dispos.* 2007;35(2):234–239. Available at: http://doi.org/10.1124/dmd.106.013045
63. Lai XJ, Zhang L, Li JS, et al. Comparative pharmacokinetic and bioavailability studies of three salvianolic acids after the administration of Salviae miltiorrhizae alone or with synthetical borneol in rats. *Fitoterapia.* 2011;82(6):883–888. Available at: http://doi.org/10.1016/j.fitote.2011.04.015
64. Alegría-Herrera E, Herrera-Ruiz M, Román-Ramos R, et al. Effect of Ocimum basilicum, Ocimum selloi, and Rosmarinic Acid on Cerebral Vascular Damage in a Chronic Hypertension Model. *Biol Pharm Bull.* 2019;42(2):201–211. Available at: http://doi.org/10.1248/bpb.b18-00574
65. Liu Q, Tian J, Xu Y, Li C, Meng X, Fu F. Protective Effect of RA on Myocardial Infarction-Induced Cardiac Fibrosis via AT1R/p38 MAPK Pathway Signaling and Modulation of the

ACE2/ACE Ratio. *J Agric Food Chem.* 2016;64(35):6716–6722. Available at: http://doi.org/10.1021/acs.jafc.6b03001
66. 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(5):514–521. Available at: http://doi.org/10.1097/FJC.0b013e31822c265d
67. Ferreira LG, Evora PRB, Capellini VK, et al. Effect of rosmarinic acid on the arterial blood pressure in normotensive and hypertensive rats: Role of ACE. *Phytomedicine.* 2018;38:158–165. Available at: http://doi.org/10.1016/j.phymed.2017.02.006
68. Li QL, Li BG, Zhang Y, Gao XP, Li CQ, Zhang GL. Three angiotensin-converting enzyme inhibitors from Rabdosia coetsa. *Phytomedicine.* 2008;15(5):386–388. Available at: http://doi.org/10.1016/j.phymed.2007.09.013
69. Böhm F, Pernow J. The importance of endothelin-1 for vascular dysfunction in cardiovascular disease. *Cardiovasc Res.* 2007;76(1):8–18. Available at: http://doi.org/10.1016/j.cardiores.2007.06.004
70. Wicha P, Tocharus J, Nakaew A, Pantan R, Suksamrarn A, Tocharus C. Ethyl rosmarinate relaxes rat aorta by an endothelium-independent pathway. *Eur J Pharmacol.* 2015;766:9–15. Available at: http://doi.org/10.1016/j.ejphar.2015.09.003
71. Fernández LF, Palomino OM, Frutos G. Effectiveness of Rosmarinus officinalis essential oil as antihypotensive agent in primary hypotensive patients and its influence on health-related quality of life. *J Ethnopharmacol.* 2014;151(1):509–516. Available at: http://doi.org/10.1016/j.jep.2013.11.006
72. Somova LI, Shode FO, Mipando M. Cardiotonic and antidysrhythmic effects of oleanolic and ursolic acids, methyl maslinate and uvaol. *Phytomedicine.* 2004;11(2–3):121–129. Available at: http://doi.org/10.1078/0944-7113-00329
73. Aguirre-Crespo F, Vergara-Galicia J, Villalobos-Molina R, Javier López-Guerrero J, Navarrete-Vázquez G, Estrada-Soto S. Ursolic acid mediates the vasorelaxant activity of Lepechinia caulescens via NO release in isolated rat thoracic aorta. *Life Sci.* 2006;79(11):1062–1068. Available at: http://doi.org/10.1016/j.lfs.2006.03.006
74. Steinkamp-Fenske K, Bollinger L, Völler N, et al. Ursolic acid from the Chinese herb danshen (Salvia miltiorrhiza L.) upregulates eNOS and downregulates Nox4 expression in human endothelial cells. *Atherosclerosis.* 2007;195(1):e104–e111. Available at: http://doi.org/10.1016/j.atherosclerosis.2007.03.028
75. Li D, Ren D, Luo Y, Yang X. Protective effects of ursolic acid against hepatotoxicity and endothelial dysfunction in mice with chronic high choline diet consumption. *Chem Biol Interact.* 2016;258:102–107. Available at: http://doi.org/10.1016/j.cbi.2016.08.019
76. Al-Taweel AM, Raish M, Perveen S, et al. Nepeta deflersiana attenuates isoproterenol-induced myocardial injuries in rats: Possible involvement of oxidative stress, apoptosis, inflammation through nuclear factor (NF)-κB downregulation. *Phytomedicine.* 2017;34:67–75. Available at: http://doi.org/10.1016/j.phymed.2017.08.003
77. Mu H, Liu H, Zhang J, et al. Ursolic acid prevents doxorubicin-induced cardiac toxicity in mice through eNOS activation and inhibition of eNOS uncoupling. *J Cell Mol Med.* 2019;23(3):2174–2183. Available at: http://doi.org/10.1111/jcmm.14130
78. Rafiee P, Rasaei N, Amini MR, et al. The effects of ursolic acid on cardiometabolic risk factors: a systematic review and meta-analysis. *Future Cardiol.* 2024;20(3):151–161. Available at: http://doi.org/10.1080/14796678.2024.2349476
79. 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(7):1066–1078. Available at: http://doi.org/10.1016/j.bcp.2005.06.026
80. Kumar D, Jugdutt BI. Apoptosis and oxidants in the heart. *J Lab Clin Med.* 2003;142(5):288–297. Available at: http://doi.org/10.1016/S0022-2143(03)00148-3
81. Diao C, Chen Z, Qiu T, et al. Inhibition of PRMT5 Attenuates Oxidative Stress-Induced Pyroptosis via Activation of the Nrf2/HO-1 Signal Pathway in a Mouse Model of Renal Ischemia-Reperfusion Injury. *Oxid Med Cell Longev.* 2019;2019:2345658. Available at: http://doi.org/10.1155/2019/2345658
82. Hu S, Liu B, Yang M, et al. Carnosic acid protects against doxorubicin-induced cardiotoxicity through enhancing the Nrf2/HO-1 pathway. *Food Funct.* 2023;14(8):3849–3862. Available at: http://doi.org/10.1039/D2FO03904D
83. Quan W, Liu HX, Zhang W, et al. Cardioprotective effect of rosmarinic acid against myocardial ischaemia/reperfusion injury via suppression of the NF-κB inflammatory signalling pathway and ROS production in mice. *Pharm Biol.* 2021;59(1):222–231. Available at: http://doi.org/10.1080/13880209.2021.1878236
84. Senthil S, Chandramohan G, Pugalendi KV. Isomers (oleanolic and ursolic acids) differ in their protective effect against isoproterenol-induced myocardial ischemia in rats. *Int J Cardiol.* 2007;119(1):131–133. Available at: http://doi.org/10.1016/j.ijcard.2006.07.108
85. Radhiga T, Rajamanickam C, Sundaresan A, Ezhumalai M, Pugalendi KV. Effect of ursolic acid treatment on apoptosis and DNA damage in isoproterenol-induced myocardial infarction. *Biochimie.* 2012;94(5):1135–1142. Available at: http://doi.org/10.1016/j.biochi.2012.01.015
86. Radhiga T, Senthil S, Sundaresan A, Pugalendi KV. Ursolic acid modulates MMPs, collagen-I, α-SMA, and TGF-β expression in isoproterenol-induced myocardial infarction in rats. *Hum Exp Toxicol.* 2019;38(7):785–793. Available at: http://doi.org/10.1177/0960327119842620
87. Senthil S, Sridevi M, Pugalendi KV. Protective effect of ursolic Acid against myocardial ischemia induced by isoproterenol in rats. *Toxicol Mech Methods.* 2007;17(1):57–65. Available at: http://doi.org/10.1080/15376510600822649
88. Sahu BD, Putcha UK, Kuncha M, Rachamalla SS, Sistla R. Carnosic acid promotes myocardial antioxidant response and prevents isoproterenol-induced myocardial oxidative stress and apoptosis in mice. *Mol Cell Biochem.* 2014;394(1–2):163–176. Available at: http://doi.org/10.1007/s11010-014-2092-5
89. Murino Rafacho BP, Portugal Dos Santos P, Gonçalves AF, et al. Rosemary supplementation (Rosmarinus oficinallis L.) attenuates cardiac remodeling after myocardial infarction in rats. *PLoS One.* 2017;12(5):e0177521. Available at: http://doi.org/10.1371/journal.pone.0177521
90. Lal H, Ahmad F, Zhou J, et al. Cardiac fibroblast glycogen synthase kinase-3β regulates ventricular remodeling and dysfunction in ischemic heart. *Circulation.* 2014;130(5):419–430. Available at: http://doi.org/10.1161/CIRCULATIONAHA.113.008364
91. Zhang X, Ma ZG, Yuan YP, et al. Rosmarinic acid attenuates cardiac fibrosis following long-term pressure overload via AMPKα/Smad3 signaling. *Cell Death Dis.* 2018;9(2):102. Available at: http://doi.org/10.1038/s41419-017-0123-3

92. Yang MD, Chiang YM, Higashiyama R, et al. Rosmarinic acid and baicalin epigenetically derepress peroxisomal proliferator-activated receptor γ in hepatic stellate cells for their antifibrotic effect. *Hepatology*. 2012;55(4):1271–1281. Available at: http://doi.org/10.1002/hep.24792
93. Joardar S, Dewanjee S, Bhowmick S, et al. Rosmarinic Acid Attenuates Cadmium-Induced Nephrotoxicity via Inhibition of Oxidative Stress, Apoptosis, Inflammation and Fibrosis. *Int J Mol Sci.* 2019;20(8):2027. Available at: http://doi.org/10.3390/ijms20082027
94. 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(11):2098–2105. Available at: http://doi.org/10.3945/jn.108.090431
95. Diao J, Zhao H, You P, et al. Rosmarinic acid ameliorated cardiac dysfunction and mitochondrial injury in diabetic cardiomyopathy mice via activation of the SIRT1/PGC-1α pathway. *Biochem Biophys Res Commun.* 2021;546:29–34. Available at: http://doi.org/10.1016/j.bbrc.2021.01.086
96. Yang Y, Li C, Xiang X, et al. Ursolic acid prevents endoplasmic reticulum stress-mediated apoptosis induced by heat stress in mouse cardiac myocytes. *J Mol Cell Cardiol.* 2014;67:103–111. Available at: http://doi.org/10.1016/j.yjmcc.2013.12.018
97. Bryk D, Olejarz W, Zapolska-Downar D. The role of oxidative stress and NADPH oxidase in the pathogenesis of atherosclerosis. *Postepy Hig Med Dosw (Online)*. 2017;71:57–68. Available at: http://doi.org/10.5604/17322693.1229823
98. Kong P, Christia P, Frangogiannis NG. The pathogenesis of cardiac fibrosis. *Cell Mol Life Sci.* 2014;71(4):549–574. Available at: http://doi.org/10.1007/s00018-013-1349-6
99. Gao X, Zhang Z, Li X, et al. Ursolic Acid Improves Monocrotaline-Induced Right Ventricular Remodeling by Regulating Metabolism. *J Cardiovasc Pharmacol.* 2020;75(6):545–555. Available at: http://doi.org/10.1097/FJC.0000000000000815
100. Li W, Wu X, Li M, et al. Cardamonin Alleviates Pressure Overload-induced Cardiac Remodeling and Dysfunction Through Inhibition of Oxidative Stress. *J Cardiovasc Pharmacol.* 2016;68(6):441–451. Available at: http://doi.org/10.1097/FJC.0000000000000430
101. Hingtgen SD, Tian X, Yang J, et al. Nox2-containing NADPH oxidase and Akt activation play a key role in angiotensin II-induced cardiomyocyte hypertrophy. *Physiol Genomics.* 2006;26(3):180–191. Available at: http://doi.org/10.1152/physiolgenomics.00029.2005
102. Matsushima S, Kuroda J, Zhai P, et al. Tyrosine kinase FYN negatively regulates NOX4 in cardiac remodeling. *J Clin Invest.* 2016;126(9):3403–3416. Available at: http://doi.org/10.1172/JCI85624
103. Bénard L, Oh JG, Cacheux M, et al. Cardiac Stim1 Silencing Impairs Adaptive Hypertrophy and Promotes Heart Failure Through Inactivation of mTORC2/Akt Signaling. *Circulation.* 2016;133(15):1458–1471. Available at: http://doi.org/10.1161/CIRCULATIONAHA.115.020678
104. Li J, Kritzer MD, Michel JJC, et al. Anchored p90 ribosomal S6 kinase 3 is required for cardiac myocyte hypertrophy. *Circ Res.* 2013;112(1):128–139. Available at: http://doi.org/10.1161/CIRCRESAHA.112.276162
105. Wei YJ, Xu HJ, Chen JJ, et al. Carnosic acid protects against pressure overload-induced cardiac remodelling by inhibiting the AKT/GSK3β/NOX4 signalling pathway. *Exp Ther Med.* 2020;20(4):3709–3719. Available at: http://doi.org/10.3892/etm.2020.9109
106. Li L, Tian JW, Liang XG. Regression of atherosclerosis by Rosmarinic acid via regulating lipid metabolism and anti-inflammatory actions. *J Mol Cell Cardiol.* 2008;44(4):719. Available at: http://doi.org/10.1016/j.yjmcc.2008.02.021
107. Wan Z, Fan Y, Liu X, et al. NLRP3 inflammasome promotes diabetes-induced endothelial inflammation and atherosclerosis. *Diabetes Metab Syndr Obes.* 2019;12:1931–1942. Available at: http://doi.org/10.2147/dmso.S222053
108. Nyandwi JB, Ko YS, Jin H, Yun SP, Park SW, Kim HJ. Rosmarinic acid inhibits oxLDL-induced inflammasome activation under high-glucose conditions through downregulating the p38-FOXO1-TXNIP pathway. *Biochem Pharmacol.* 2020;182:114246. Available at: http://doi.org/10.1016/j.bcp.2020.114246
109. Nyandwi JB, Ko YS, Jin H, Yun SP, Park SW, Kim HJ. Rosmarinic Acid Increases Macrophage Cholesterol Efflux through Regulation of ABCA1 and ABCG1 in Different Mechanisms. *Int J Mol Sci.* 2021;22(16):8791. Available at: http://doi.org/10.3390/ijms22168791
110. Nyandwi JB, Ko YS, Jin H, Yun SP, Park SW, Kim HJ. Rosmarinic Acid Exhibits a Lipid-Lowering Effect by Modulating the Expression of Reverse Cholesterol Transporters and Lipid Metabolism in High-Fat Diet-Fed Mice. *Biomolecules.* 2021;11(10):1470. Available at: http://doi.org/10.3390/biom11101470
111. Straub LG, Scherer PE. Metabolic Messengers: Adiponectin. *Nat Metab.* 2019;1(3):334–339. Available at: http://doi.org/10.1038/s42255-019-0041-z
112. Wentworth JM, Zhang JG, Bandala-Sanchez E, et al. Interferon-gamma released from omental adipose tissue of insulin-resistant humans alters adipocyte phenotype and impairs response to insulin and adiponectin release. *Int J Obes (Lond).* 2017;41(12):1782–1789. Available at: http://doi.org/10.1038/ijo.2017.180
113. Vasileva LV, Savova MS, Tews D, Wabitsch M, Georgiev MI. Rosmarinic acid attenuates obesity and obesity-related inflammation in human adipocytes. *Food Chem Toxicol.* 2021;149:112002. Available at: http://doi.org/10.1016/j.fct.2021.112002
114. Ullevig SL, Zhao Q, Zamora D, Asmis R. Ursolic acid protects diabetic mice against monocyte dysfunction and accelerated atherosclerosis. *Atherosclerosis.* 2011;219(2):409–416. Available at: http://doi.org/10.1016/j.atherosclerosis.2011.06.013
115. Nguyen HN, Ahn YJ, Medina EA, Asmis R. Dietary 23-hydroxy ursolic acid protects against atherosclerosis and obesity by preventing dyslipidemia-induced monocyte priming and dysfunction. *Atherosclerosis.* 2018;275:333–341. Available at: http://doi.org/10.1016/j.atherosclerosis.2018.06.882
116. Leng S, Iwanowycz S, Saaoud F, et al. Ursolic acid enhances macrophage autophagy and attenuates atherogenesis. *J Lipid Res.* 2016;57(6):1006–1016. Available at: http://doi.org/10.1194/jlr.M065888
117. Jiang Q, Han Y, Gao H, Tian R, Li P, Wang C. Ursolic acid induced anti-proliferation effects in rat primary vascular smooth muscle cells is associated with inhibition of microRNA-21 and subsequent PTEN/PI3K. *Eur J Pharmacol.* 2016;781:69–75. Available at: http://doi.org/10.1016/j.ejphar.2016.04.001
118. Lin YT, Yu YM, Chang WC, Chiang SY, Chan HC, Lee MF. Ursolic acid plays a protective role in obesity-induced cardiovascular diseases. *Can J Physiol Pharmacol.* 2016;94(6):627–633. Available at: http://doi.org/10.1139/cjpp-2015-0407
119. Zeller I, Wiedemann D, Schwaiger S, et al. Inhibition of cell surface expression of endothelial adhesion molecules by ursolic acid prevents intimal hyperplasia of venous bypass grafts in rats. *Eur J Cardiothorac Surg.* 2012;42(5):878–884. Available at:

http://doi.org/10.1093/ejcts/ezs128
120. Takada K, Nakane T, Masuda K, Ishii H. Ursolic acid and oleanolic acid, members of pentacyclic triterpenoid acids, suppress TNF-α-induced E-selectin expression by cultured umbilical vein endothelial cells. *Phytomedicine.* 2010;17(14):1114–1119. Available at: http://doi.org/10.1016/j.phymed.2010.04.006
121. Yu YM, Tsai CC, Tzeng YW, Chang WC, Chiang SY, Lee MF. Ursolic acid suppresses leptin-induced cell proliferation in rat vascular smooth muscle cells. *Can J Physiol Pharmacol.* 2017;95(7):811–818. Available at: http://doi.org/10.1139/cjpp-2016-0398
122. Chang Y, Zhou S, Li E, et al. Fragment-based discovery of novel pentacyclic triterpenoid derivatives as cholesteryl ester transfer protein inhibitors. *Eur J Med Chem.* 2017;126:143–153. Available at: http://doi.org/10.1016/j.ejmech.2016.09.098
123. Chen C, Sun R, Sun Y, et al. Synthesis, biological evaluation and SAR studies of ursolic acid 3β-ester derivatives as novel CETP inhibitors. *Bioorg Med Chem Lett.* 2020;30(2):126824. Available at: http://doi.org/10.1016/j.bmcl.2019.126824
124. Messner B, Zeller I, Ploner C, et al. Ursolic acid causes DNA-damage, P53-mediated, mitochondria- and caspase-dependent human endothelial cell apoptosis, and accelerates atherosclerotic plaque formation in vivo. *Atherosclerosis.* 2011;219(2):402–408. Available at: http://doi.org/10.1016/j.atherosclerosis.2011.05.025
125. Hua WJ, Hua WX, Nan FY, Jiang WA, Yan C. The influence of herbal medicine ursolic acid on the uptake of rosuvastatin mediated by OATP1B1*1a and *5. *Eur J Drug Metab Pharmacokinet.* 2014;39(3):221–230. Available at: http://doi.org/10.1007/s13318-014-0187-8
126. Romo-Vaquero M, Selma MV, Larrosa M, et al. A rosemary extract rich in carnosic acid selectively modulates caecum microbiota and inhibits β-glucosidase activity, altering fiber and short chain fatty acids fecal excretion in lean and obese female rats. *PLoS One.* 2014;9(4):e94687. Available at: http://doi.org/10.1371/journal.pone.0094687
127. He X, Zhang M, Li ST, et al. Alteration of gut microbiota in high-fat diet-induced obese mice using carnosic acid from rosemary. *Food Sci Nutr.* 2022;10(7):2325–2332. Available at: http://doi.org/10.1002/fsn3.2841
128. Gaya M, Repetto V, Toneatto J, Anesini C, Piwien-Pilipuk G, Moreno S. Antiadipogenic effect of carnosic acid, a natural compound present in Rosmarinus officinalis, is exerted through the C/EBPs and PPARγ pathways at the onset of the differentiation program. *Biochim Biophys Acta.* 2013;1830(6):3796–3806. Available at: http://doi.org/10.1016/j.bbagen.2013.03.021
129. Wang T, Takikawa Y, Tabuchi T, Satoh T, Kosaka K, Suzuki K. Carnosic acid (CA) prevents lipid accumulation in hepatocytes through the EGFR/MAPK pathway. *J Gastroenterol.* 2012;47(7):805–813. Available at: http://doi.org/10.1007/s00535-012-0546-7
130. Liao CH, Hung HC, Lai CN, et al. Carnosic acid and rosemary extract reversed the lipid accumulation induced by bisphenol A in the 3T3-L1 preadipocytes and C57BL/6J mice via SIRT1/FoxO1 pathway. *Food Chem Toxicol.* 2023;179:113996. Available at: http://doi.org/10.1016/j.fct.2023.113996
131. Sinkovic A, Suran D, Lokar L, et al. Rosemary extracts improve flow-mediated dilatation of the brachial artery and plasma PAI-1 activity in healthy young volunteers. *Phytother Res.* 2011;25(3):402–407. Available at: http://doi.org/10.1002/ptr.3276
132. Posadas SJ, Caz V, Largo C, et al. Protective effect of supercritical fluid rosemary extract, Rosmarinus officinalis, on antioxidants of major organs of aged rats. *Exp Gerontol.* 2009;44(6–7):383–389. Available at: http://doi.org/10.1016/j.exger.2009.02.015
133. Hegazy AM, Abdel-Azeem AS, Zeidan HM, Ibrahim KS, Sayed EE. Hypolipidemic and hepatoprotective activities of rosemary and thyme in gentamicin-treated rats. *Hum Exp Toxicol.* 2018;37(4):420–430. Available at: http://doi.org/10.1177/0960327117710534
134. Jun HJ, Lee JH, Jia Y, et al. Melissa officinalis essential oil reduces plasma triglycerides in human apolipoprotein E2 transgenic mice by inhibiting sterol regulatory element-binding protein-1c-dependent fatty acid synthesis. *J Nutr.* 2012;142(3):432–440. Available at: http://doi.org/10.3945/jn.111.152538
135. Tu Z, Moss-Pierce T, Ford P, Jiang TA. Rosemary (Rosmarinus officinalis L.) extract regulates glucose and lipid metabolism by activating AMPK and PPAR pathways in HepG2 cells. *J Agric Food Chem.* 2013;61(11):2803–2810. Available at: http://doi.org/10.1021/jf400298c