# 迷迭香酸在心血管疾病防治中的作用机制研究进展

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**摘要**: 随着社会经济的飞速发展和人类生活水平的持续提高, 心血管疾病 (cardiovascular disease, CVD) 的发病率、致死率及复发率逐年上升, 严重影响着人们的生命健康。常规的治疗药物对致残率的改善有限, 因此, 寻求新的治疗药物及作用靶点成为目前研究的热点之一。近年来, 天然化合物迷迭香酸 (rosmarinic acid, RA) 在CVD的治疗作用备受关注, 其能够通过调控多条信号通路防治CVD, 发挥抗氧化、抗细胞凋亡、抗炎、抗血小板聚集以及抗凝血、保护内皮功能等生理活性。本文系统梳理了RA在CVD防治中的作用, 对其作用机制进行归纳分析, 以期为深入挖掘RA在CVD中防治价值及进一步开发成为防治药物提供科学依据和重要支撑。

**关键词**: 迷迭香酸; 心血管; 抗炎; 抗氧化; 抗血小板聚集; 抗凝血; 保护内皮功能

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# Research progress on the mechanism of action of rosmarinic acid in the prevention of cardiovascular diseases

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**Abstract**: With the rapid development of social economy and the continuous improvement of human living standard, the incidence, fatality and recurrence rates of cardiovascular disease (CVD) are increasing year by year, which seriously affects people's life and health. Conventional therapeutic drugs have limited improvement on the disability rate, so the search for new therapeutic drugs and action targets has become one of the hotspots of current research. In recent years, the therapeutic role of the natural compound rosmarinic acid (RA) in CVD has attracted much attention, which is capable of preventing CVD by modulating multiple signalling pathways and exerting physiological activities such as antioxidant, anti-apoptotic, anti-inflammatory, anti-platelet aggregation, as well as anti-coagulation and endothelial function protection. In this paper, the role of RA in the prevention of CVD is systematically sorted out, and its mechanism of action is summarised and analysed, with a view to providing a scientific basis and important support for the in-depth exploration of the prevention value of RA in CVD and its further development as a prevention drug.

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**Key words**: rosmarinic acid; cardiovascular; anti-inflammatory; antioxidant; antiplatelet aggregation; anticoagulation; protection of endothelial function

心血管疾病 (cardiovascular disease, CVD) 因其极高的发病率和死亡率, 严重威胁个人的身心健康和生活质量而备受关注[1]。目前用于预防和治疗CVD的药物虽然具有明确的靶标和一定的疗效, 但存在靶点单一和产生毒副作用的问题。因此, 研究更有效、更安全的控制CVD的药物至关重要。

迷迭香酸 (rosmarinic acid, RA) 是一种天然水溶性多酚类化合物, 意大利化学家首次从迷迭香 (*Rosmarinus officinalis* Linn) 中提取分离得到, 并将其命名为迷迭香酸[2], 结构式见图1。常见于丹参、紫苏、夏枯草、鼠尾草等中药材中[3], 同时也是芪参益气滴丸、复方丹参滴丸、丹红化瘀口服液、注射用丹参多酚酸等中成药的主要成分[4-7]。临床上常将这些中成药用于治疗冠心病、心肌梗死及缺血性心脏病等CVD[8-10]。近些年, RA在CVD中的独特作用引起了人们的极大关注。尽管RA具有众多药理活性, 但研究者仍在探索其作用机制。本文从氧化应激、细胞凋亡、炎症、血小板聚集与凝血作用、内皮功能等方面梳理RA在CVD治疗中的作用, 对其作用机制进行系统的整理分析, 以期为深入挖掘RA在CVD治疗过程中的价值及进一步开发成为治疗药物提供科学依据和重要支撑。

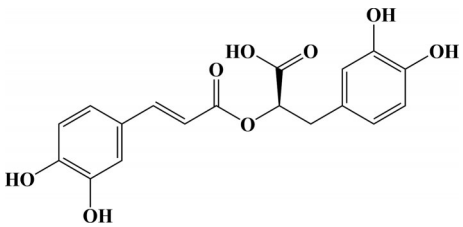


**Figure 1**　Chemical structural formula of rosmarinic acid

## 1　抗氧化作用

在各种类型的CVD (心力衰竭、高血压、外周动脉疾病和脑卒中) 中, 血液循环和组织中普遍存在以活性氧化物形式的高水平氧化应激[11]。核因子-E2相关因子2 (nuclearfactor erythroid derived 2-like 2, Nrf2) 是一种重要而广泛的抗氧化转录因子, 可能有助于CVD的发病和维持。Nrf2/Kelch样ECH (epichlorohydrin, 环氧丙氯烷) 关联蛋白-1 (Kelch-like ECH associated protein-1, Keap1) 通路是抗氧化应激的主要通路之一, 与CVD的发生发展关系密切[12]。在正常情况下, Nrf2与Keap1结合, 使其处于失活状态。当细胞受到氧化应激时, Keap1与Nrf2解离, Nrf2得以活化并转移到细胞核, 诱导一系列抗氧化基因的表达[13]。

迷迭香酸可以通过多种途径激活Nrf2/Keap1通路活性。在脑缺血再灌注损伤小鼠模型中, 40 mg·kg$^{-1}$迷迭香酸能够升高脑组织中超氧化物歧化酶1 (superoxide dismutase 1, SOD1)、超氧化物歧化酶2 (superoxide dismutase 2, SOD2)、血红素加氧酶1 (heme oxygenase 1, HO-1)、Nrf2蛋白的表达, 从而通过激活Nrf2信号通路, 减少机体氧化损伤[14]。在另一项心肌缺血小鼠模型中, 迷迭香酸可使心肌细胞中丙二醛 (malondialdehyde, MDA) 含量降低、SOD活力增加, 从而提高抗氧化酶活性, 降低自由基水平, 抑制脂质过氧化反应[15]。在动脉损伤后, 血管平滑肌细胞 (VSMCs) 表现为Nrf2/抗氧化反应元件 (antioxidant response element, ARE) 信号通路的抑制, 迷迭香酸的治疗作用可通过激活Nrf2/ARE信号通路逆转了这一特征, 具体表现为稳定Keap1蛋白, 上调HO-1、醌氧化还原酶-1 (NADPH: quinone oxidoreductase 1, NQO1)、谷氨酸半胱氨酸连接酶 (glutamate cysteine ligase regulatory subunit, GCLM) 和谷胱甘肽-*S*-转移酶 (glutathione *S*-transferase, GST) 蛋白水平; 促进典型的Nrf2核易位; 防止VSMCs的氧化应激损伤[16] (图2)。迷迭香酸的抗氧化作用与其结构有关, Nakamura等[17]认为邻二酚羟基是清除自由基活性的物质基础, 而且C3位的共轭双键具有增效作用。

因此, 迷迭香酸对于细胞氧化水平的影响, 主要激活了Keap1/Nrf2/ARE信号通路活性, 进而提高下游抗氧化因子, 降低氧化因子的表达以维持机体的氧化/抗氧化平衡, 其具体调控机制有待深入探讨。

## 2　抗凋亡作用

心肌缺血时, 心肌组织不仅缺氧和代谢障碍, 同时毒性产物蓄积, 引起缺血性损伤, 若继续发展导致心肌细胞死亡[18]。细胞死亡是所有生物体的基本过程, 通过不同的机制发生。近年来, 普遍认为程序性细胞死亡的主要类型有3种, 分别是细胞凋亡、细胞焦亡和坏死性凋亡[19]。细胞凋亡是一种主动性的基因控制的细胞死亡形式, 在真核生物正常发育和维持机体平衡的过程中负责对细胞进行程序性清除。凋亡的启动与抑制受多种内源性及外源性信号的刺激, 而且在其发生过程中, 有许多因子参与。这一途径由抗凋亡蛋白B细胞白血病/淋巴瘤-2 (B cell lymphoma-2, Bcl-2) 蛋白

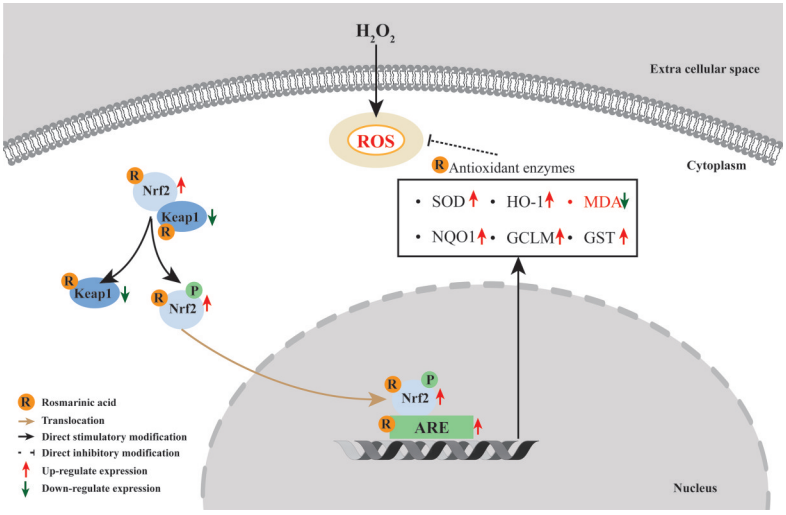


**Figure 2** Mechanism of antioxidant action of rosmarinic acid in cardiovascular disease. Nrf2: Nuclearfactor erythroid derived 2-like 2; Keap1: Kelch-like ECH associated protein-1; SOD1: Superoxide dismutase 1; SOD2: Superoxide dismutase 2; HO-1: Heme oxygenase 1; MDA: Malondialdehyde; ARE: Antioxidant response element; NQO1: NADPH: quinone oxidoreductase 1; GCLM: Glutamate cysteine ligase regulatory subunit; GST: Glutathione *S*-transferase

家族控制, 该家族包含促凋亡和抗凋亡两种成员, 可平衡细胞生死[20]。

有研究显示, 迷迭香酸能够拮抗 $H_2O_2$ 诱导血管平滑肌细胞凋亡, 其作用机制可能与升高细胞中 Bcl-2/凋亡蛋白 (Bcl-2-associated X, Bax) 比值, 减少凋亡相关因子 (recombinant factor related apoptosis, Fas)、凋亡相关因子配体 (recombinant factor related apoptosis ligand, Fas L) 蛋白表达有关[21]。在 $H_2O_2$ 诱导的人脐静脉内皮细胞株 ECV304 中, 1～10 μmol·L$^{-1}$ 迷迭香酸可以抑制内皮细胞凋亡, 与上调 Bcl-2 蛋白水平, 抑制 Bax 蛋白和半胱氨酸的天冬氨酸蛋白水解酶-3 (cysteinyl aspartate specific proteinase-3, caspase-3) 蛋白的表达有关[22]。此外, 另有研究显示, 迷迭香酸能够通过参与磷脂酰肌醇 3-激酶 (phosphatidylinositol 3 kinase, PI3K)/磷酸激酶 B (protein kinase B, AKT) 信号通路, 调控 Bax 和 Bcl-2 等蛋白表达, 抑制心肌细胞凋亡, 从而有效延缓大鼠心肌缺血再灌注损伤 (MIRI) 动物模型心肌损伤标志物水平的释放, 对心肌细胞产生保护作用[23]。在大鼠冠脉结扎心肌缺血模型中, 迷迭香酸同样能够上调抗凋亡蛋白 Bcl-2 和下调促凋亡蛋白 Bax 的表达[15], 说明迷迭香酸抗心肌缺血的机制可能与其对凋亡蛋白的调节密切相关。另外, 在多柔比星 (DOX) 诱导的心脏毒性小鼠模型中, 心脏成纤维细胞 (CFs) 衍生的 Fas L 是 DOX 诱导的心肌细胞凋亡的原因, 研究发现, 迷迭香酸处理可抑制活化 T 细胞核因子 (nuclear factor of activated T cell, NFAT) 活化和金属蛋白酶 7 (matrix metalloproteinase 7, MMP7) 表达, 降低 CFs 中 Fas L 的表达及其向条件培养基的释放, 并通过 CFs 对新生大鼠心肌细胞 (CMs) 发挥抗凋亡作用[24]。在 $H_2O_2$ 诱导的大鼠骨髓间充质干细胞 (rBMSCs) 中, 迷迭香酸预处理显著降低细胞凋亡率, 下调 caspase-3、半胱氨酸的天冬氨酸蛋白水解酶-9 (cysteinyl aspartate specific proteinase-9, caspase-9)、Bax/Bcl-2 水平, 上调 p-PI3K 水平。表明迷迭香酸可通过部分调节 PI3K/AKT 信号通路来保护 rBMSCs 免受 $H_2O_2$ 诱导的细胞凋亡, 可作为一种潜在的抗凋亡药物用于 CVD 的治疗[25]。近年来, 研究还发现迷迭香酸的衍生物迷迭香酸正丁酯 (RABE), 可显著保护人骨髓神经母细胞瘤细胞 (SH-SY5Ys) 免受氧葡萄糖剥夺 (OGD) 诱导的细胞死亡。用 RABE (1 和 10 μmol·L$^{-1}$) 进行预处理可剂量依赖性地降低细胞凋亡速率, 下调促凋亡蛋白 Bax 和肿瘤蛋白 p53 (tumor protein 53, p53) 的表达, 并上调抗凋亡蛋白磷酸化死亡相关蛋白激酶 (death-associated protein kinase, DAPK) 的表达[26] (图 3)。

因此, 迷迭香酸对细胞的凋亡作用涉及多方面, 主要抑制 Fas/FasL、PI3K/AKT、NFAT、DAPK 等通路, 下调促凋亡蛋白 Bax、caspase-3、caspase-9、p53 的表达, 上调抗凋亡蛋白 Bcl-2 的表达, 还可以通过抑制 MMP-7 和 MMP-9 等金属蛋白酶的表达而抑制细胞凋亡。

## 3 减轻炎症反应

炎症涉及广泛的病理生理过程, 是机体应对某些刺激时作出的防御反应, 当炎症反应处于急性期时, 一些免疫细胞就会在细胞因子等因素介导下快速地聚集

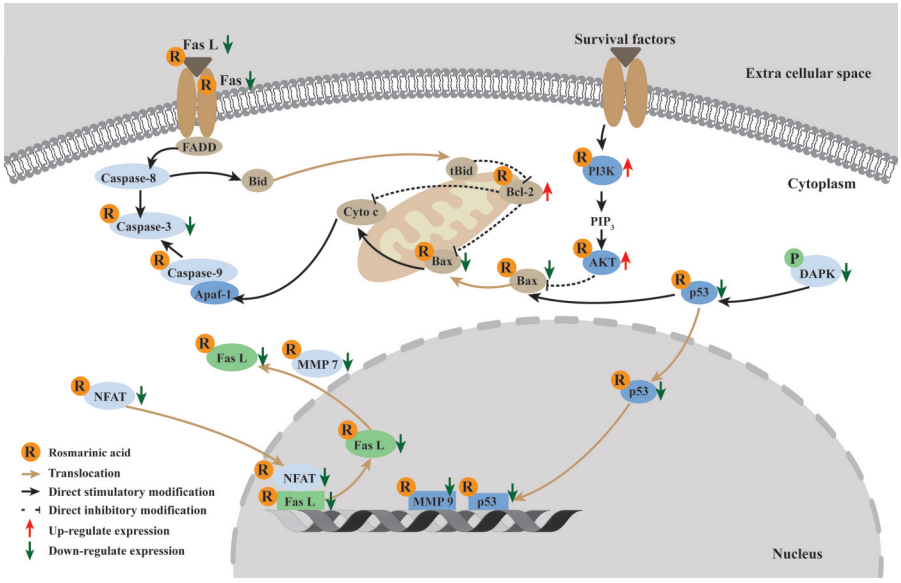


**Figure 3**　Mechanism of anti-apoptotic action of rosmarinic acid in cardiovascular disease. Bcl-2: B cell lymphoma-2; Bax: Bcl-2-associated X; Fas: Recombinant factor related apoptosis; Fas L: Recombinant factor related apoptosis ligand; Caspase-3: Cysteinyl aspartate specific proteinase-3; PI3K: Phosphatidylinositol 3 kinase; AKT: Protein kinase B; NFAT: Nuclear factor of activated T cell; MMP7: Matrix metalloproteinase 7; Caspase-9: Cysteinyl aspartate specific proteinase-9; DAPK: Death-associated protein kinase; p53: Tumor protein 53

在受损位置。炎症反应在动脉粥样硬化的发生、发展过程中起到重要作用[27]。

有研究通过氧糖剥夺/再灌注 (oxygen-glucose deprivation/reoxygenation, OGD/R) 的方法刺激小鼠心肌细胞 HL-1, 发现迷迭香酸 (50 μmol·L$^{-1}$) 预处理可以降低 OGD/R 损伤后核因子 $\kappa$B (nuclear factor kappa-B, NF-$\kappa$B) 信号通路中关键蛋白 p-NF-$\kappa$B 和磷酸化 I$\kappa$B 激酶-$\alpha$ (phospho inhibitor of $\kappa$B alpha, p-I$\kappa$B-$\alpha$) 的表达水平[28]。硫氧还蛋白互作蛋白 (thioredoxin-interacting protein, TXNIP) 被认为是氧自由基 (reactive oxygen species, ROS) 诱导的 NOD 样受体热蛋白结构域相关蛋白 3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3) 炎症小体复合物形成和激活的有效介质, 可启动糖尿病动脉粥样硬化的发展[29]。迷迭香酸通过下调内皮细胞中磷酸化 p38 丝裂原活化蛋白激酶 (phospho p38 mitogen-activated protein kinase, p-p38 MAPK)、叉头框蛋白 O1 (forkhead box protein O1, FOXO1)、TXNIP、NLRP3 蛋白的表达, 从而减弱 NLRP3 炎症小体组装和激活, 并最终减弱内皮细胞中白细胞介素 1$\beta$ (interleukin-1$\beta$, IL-1$\beta$) 分泌。这些发现表明, 迷迭香酸通过下调 p38 MAPK-FOXO1-TXNIP 通路和抑制炎症小体活化来减轻内皮炎症反应, 从而治疗糖尿病动脉粥样硬化[30] (图 4)。

因此, 迷迭香酸减轻炎症反应, 主要通过抑制 NF-$\kappa$B、p38 MAPK-FOXO1-TXNIP 等通路, 以及 IL-1$\beta$ 等炎症因子的释放。

## 4　抗血小板聚集和抗凝血作用

血小板功能和凝血功能异常在 CVD 的发病机制中发挥着重要作用, 血小板活化和聚集的信号传导途径是治疗的主要靶点。此外, 高脂血症是 CVD 发展的一个重要危险因素。反向胆固醇转运 (reverse cholesterol transport, RCT) 过程已被证明可以缓解高脂血症并预防 CVD。

蛋白二硫化物异构酶 A3 (recombinant endoplasmic reticulum resident protein 57, ERp57) 是蛋白二硫键异构酶的成员, 在血小板聚集中具有潜在作用[31]。研究表明, 迷迭香酸能够特异性地与 ERp57 蛋白上的 Ser312、Lys366、Asp440 和 Val441 形成氢键, 从而抑制 ERp57 活性, 发挥体外抑制血小板聚集的作用[32]。此外, 通过流式细胞术分析发现, 1 μmol·L$^{-1}$ 迷迭香酸有效抑制花生四烯酸 (arachidonic acid, AA) 诱导的血小板中 P-选择素的释放, 在大鼠模型中, 5 mg·kg$^{-1}$ 口服迷迭香酸可有效抑制血栓形成[33]。P2Y 受体是血小板活化的关键因素, 也是抗血栓药物的主要靶点[34]。血小板上有两种不同的二磷酸腺苷 (adenosine diphosphate, ADP) P2Y 受体: Gq 偶联的 $P2Y_1R$ 和 Gi 偶联的 $P2Y_{12}R$。两者都有助于全血中 ADP 诱导的血小板微颗粒形成和血小板–白细胞聚集体的形成[35]。然而, 只有 $P2Y_{12}R$ 参与凝血酶或其他血小板激动剂对磷脂酰丝氨酸的暴露[36]。分子对接结果显示, $P2Y_{12}$ 受体可能是迷迭香酸和血小板的结合靶点[37]。早期有学者采用手术方法结扎大鼠下腔静脉后, 强烈的刺激造成

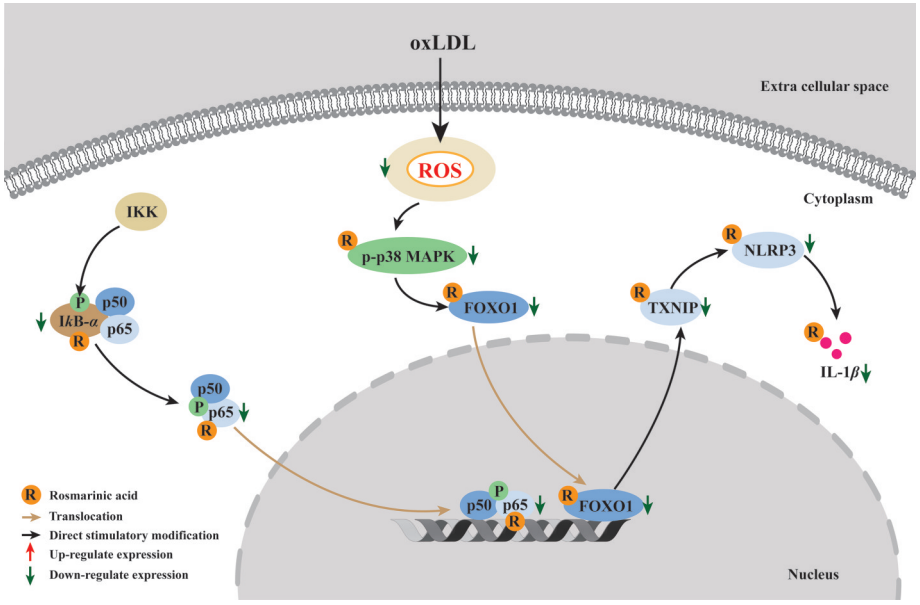


**Figure 4** Mechanism of anti-inflammatory action of rosmarinic acid in cardiovascular disease. NF-*κ*B: Nuclear factor kappa-B. p-I*κ*B-*α*: Phospho inhibitor of *κ*B alpha; ROS: Reactive oxygen species; TXNIP: Thioredoxin-interacting protein; NLRP3: NOD-like receptor thermal protein domain associated protein 3; p-p38 MAPK: Phospho p38 mitogen-activated protein kinase; FOXO1: Forkhead box protein O1; IL-1*β*: Interleukin-1*β*

了血管壁损伤, 凝血因子被激活, 同时血流中止, 促使血栓形成。证实了迷迭香酸有温和的抗血栓作用, 其机制可能与抑制血小板聚集和增强纤维蛋白溶解活性有关[38]。此外, 最近研究报道迷迭香酸具有降脂作用, 迷迭香酸治疗显著降低了高脂饲料喂养小鼠的体重、血糖、血浆总胆固醇和甘油三酯水平, 增加了肝组织中胆固醇摄取相关受体的表达水平, 包括B类Ⅰ型清道夫受体 (scavenger receptor class B type 1, SR-B1) 和低密度脂蛋白受体 (low density lipoprotein receptor, LDL-R)。此外, 迷迭香酸处理显著增加胆固醇排泄分子、ATP结合盒转运蛋白G5 (ATP binding cassette transporter G5, ABCG5) 和G8 (ATP binding cassette transporter G8, ABCG8) 以及胆固醇7*α*-羟化酶 (cholesterol 7*α*-hydroxylase, CYP7A1) 的表达, 并显著降低肝组织中胆固醇和甘油三酯水平。此外, 迷迭香酸通过单磷酸腺苷激活的蛋白激酶 [adenosine 5'-monophosphate (AMP) -activated protein kinase, AMPK] 介导的肉毒碱棕榈酰基转移酶1A (carnitine palmitoyltransferase 1A, CPT1A) 诱导作用促进脂肪酸氧化[39] (图5)。

因此, 迷迭香酸抑制血小板聚集和凝血作用, 主要通过抑制ERp57、$P2Y_{12}$等关键蛋白及P-选择素的释放, 还通过增加SR-B1、LDL-R、ABCG5/8和CYP7A1等蛋白的表达从而激活反向胆固醇转运以降低胆固醇和甘油三酯水平, 以及增加p-AMPK和CPT1A蛋白表达, 以促进脂肪酸氧化共同降低体内脂质积累。

## 5 内皮功能的保护作用

内皮细胞通过合成和释放多种内皮衍生的松弛因子, 包括血管扩张剂前列腺素、NO和内皮依赖性超极化因子, 以及内皮衍生的收缩因子, 在调节血管张力方面发挥重要作用。内皮细胞功能包括维持血管张力、血管生成、止血, 以及为机体提供一个抗氧化、抗炎和抗血栓形成的界面[40]。内皮功能障碍主要是由这些松弛介质的产生或作用减少引起的。越来越多的证据表明, 内皮功能对于确保血管稳态的正确维持至关重要, 而内皮功能障碍是与血管收缩、血栓形成和炎症状态等病理状况相关的一系列CVD的标志[41]。

在高血糖和血脂异常的情况下, 内皮功能障碍被认为是与动脉粥样硬化形成相关的初始步骤[42]。脂蛋白摄取增加和胆固醇外排减少促进了富含胆固醇的巨噬细胞源性泡沫细胞的形成, 从而加速了动脉粥样硬化病变和斑块的形成[43]。在高糖 (high glucose, HG) 条件下, 迷迭香酸可有效降低巨噬细胞中氧化型低密度脂蛋白 (oxidized low-density lipoprotein, ox-LDL) 携带的胆固醇含量。迷迭香酸增强ATP结合盒转运蛋白A1 (ATP binding cassette transporter Al, ABCA1) 和G1 (ATP binding cassette transporter G1, ABCG1) 的表达, 促进巨噬细胞胆固醇外流。在机制上, 迷迭香酸是通过Janus激酶2 (janus kinase 2, JAK2)/信号传导转录激活因子3 (signal transducer and activator of transcrip-

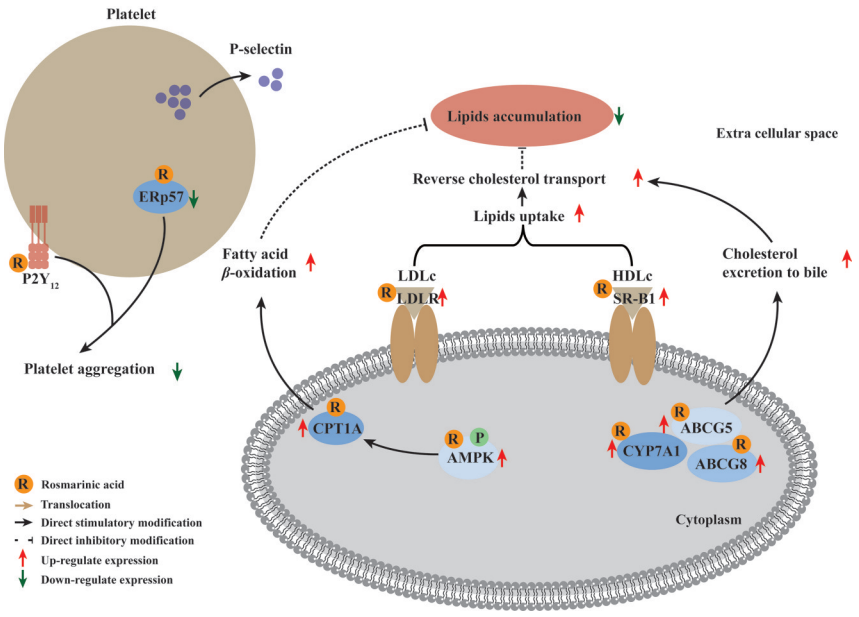


**Figure 5**　Mechanisms of antiplatelet aggregation and anticoagulant effects of rosmarinic acid in cardiovascular diseases. RCT: Reverse cholesterol transport; ERp57: Recombinant endoplasmic reticulum resident protein 57; AA: Arachidonic acid; ADP: Adenosine diphosphate; SR-B1: Scavenger receptor class B type 1; LDL-R: Low density lipoprotein receptor; ABCG5: ATP binding cassette transporter G5; ABCG8: ATP binding cassette transporter G8; CYP7A1: Cholesterol 7$\alpha$-hydroxylase; AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; CPT1A: Carnitine palmitoyltransferase 1A

tion 3, STAT3)、c-Jun 氨基末端激酶 (c-jun N-terminal kinase, JNK) 和蛋白激酶 C (protein kinase C, PKC)-p38 MAPK 对巨噬细胞中 ABCA1 的表达进行差异调控, 通过 JAK2/STAT3、JNK 和 PKC-细胞外调节蛋白激酶 1/2 (extracellular regulated protein kinases 1/2, ERK1/2)/p38 MAPK 调控巨噬细胞中 ABCG1 的表达[44]。此外, 脂多糖 (LPS) 处理后, 血管内皮细胞中的 NLRP3 表达增加, 引起细胞焦亡。迷迭香酸通过抑制细胞中 NLRP3 炎症小体的蛋白表达及转录从而提高血管内皮细胞的活力, 表明通过激活 Nrf2-NLRP3 通路, 抑制 ROS 的产生以调节细胞焦亡进程[45] (图 6)。

因此, 迷迭香酸保护内皮细胞功能、调节血管内皮

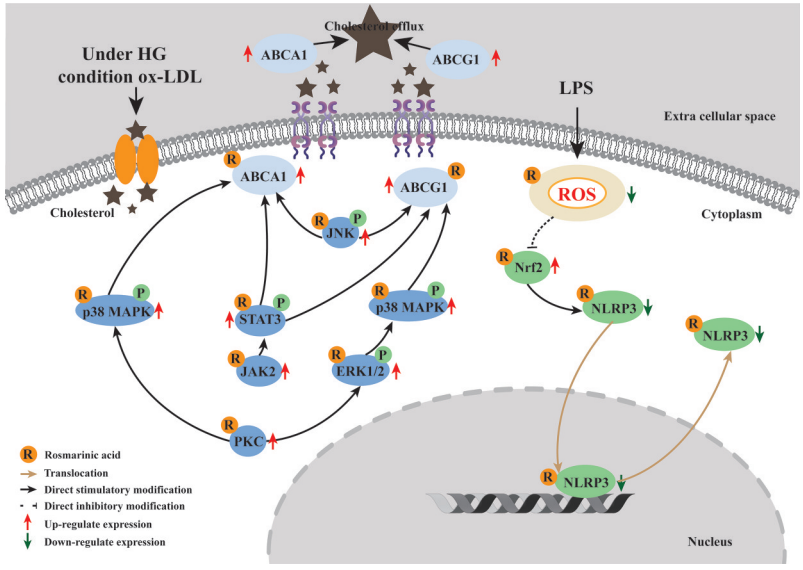


**Figure 6**　Mechanisms of protective effect of rosmarinic acid on endothelial function in cardiovascular diseases. HG: High glucose; ox-LDL: Oxidized low-density lipoprotein; ABCA1: ATP binding cassette transporter Al; ABCG1: ATP binding cassette transporter G1; JAK2: Janus kinase 2; STAT3: Signal transducer and activator of transcription 3; JNK: C-jun N-terminal kinase; PKC: Protein kinase C; ERK1/2: Extracellular regulated protein kinases 1/2

细胞稳态失衡主要通过激活JAK2/STAT3、JNK、PKC/p38 MAPK信号通路增加ABCA1的表达, 以及激活JAK2/STAT3、JNK、PKC/ERK1/2/p38 MAPK信号通路增加ABCG1的表达, 共同促进巨噬细胞中胆固醇的外排。此外, 通过激活Nrf2-NLRP3通路, 抑制ROS的产生以调节细胞焦亡进程。

## 6 结语与展望

CVD多以改善生活方式、西药以及手术治疗为主, 中医药作为中国古代科学文明的宝藏, 至今已有数千年的历史, 因理论体系不同于西方医学, 临床应用受到限制。随着人类科学技术的不断发展, 医药研究者们尝试着从分子水平阐释中医药学的治疗机制, 以期建立中西医结合防治CVD的治疗方式。

迷迭香酸治疗CVD的作用涉及多种机制 (表1), 包括抗氧化、抗凋亡、抗炎、抗血小板聚集和抗凝血作用以及保护内皮功能等多方面, 这些研究大多与血管内皮细胞稳态失衡有关, 但具体调控机制仍需进一步深入探讨。目前已有研究发现, 迷迭香酸通过激活AMPK减弱$H_2O_2$诱导的大鼠主动脉环内皮功能障碍[46], 降低了LPS和高迁移率族蛋白B1 (high mobility group box-1 protein, HMGB1) 诱导的内皮过高通透性, 并增强了暴露于LPS或HMGB1的内皮细胞之间紧密和黏附连接的稳定性[47]。因此, 有望从内皮功能障碍方面, 进一步探索CVD的发病机制以及迷迭香酸对CVD的影响。

综上, 迷迭香酸可以通过多种作用途径发挥治疗CVD的效果, 因其抗炎和抗氧化特性以及在各种危及生命的疾病 (如癌症、神经退行性变、糖尿病等) 中的作用而广受欢迎[48]。目前常用方式主要为溶液和粉末形式, 尚无法满足不同给药途径和疾病部位的需求, 且迷迭香酸作为多酚酸类化合物, 由于其水溶性强的理化性质限制了其生物利用度[49]。为进一步提高治疗效

**Table 1** Mechanisms of action of rosmarinic acid in the prevention of cardiovascular diseases. " ↑ " up-regulation, " ↓ " down-regulation

| Mechanism of action | Research object | Dosage | Effect indicator or target | Reference |
|---|---|---|---|---|
| Anti-oxidative stress | Male ICR mice (27−30 g) were subjected to ischemia-reperfusion injury with middle cerebral artery occlusion surgery | 10−40 mg·kg$^{-1}$ | SOD1, SOD2, HO-1, Nrf2 ↑ | [14] |
| | Male Wistar rats (250−280 g) were ligated with the anterior descending coronary artery to create a rat model of acute myocardial ischemia | 50−200 mg·kg$^{-1}$ | MDA ↓, SOD ↑ | [15] |
| | Vascular smooth muscle cells (VSMCs) | 25−400 μmol·L$^{-1}$ | Keap1 ↓, HO-1, NQO1, GCLM, GST ↑ | [16] |
| Antiapoptosis | $H_2O_2$ induced VSMCs | 10−40 μmol·L$^{-1}$ | Fas, Fas L ↓, Bcl-2/Bax ↑ | [21] |
| | $H_2O_2$ induced human umbilical vein endothelial cells (ECV304) | 1−10 μmol·L$^{-1}$ | Bax, caspase-3 ↓, Bcl-2 ↑ | [22] |
| | SD rats of both sexes (260−300 g), myocardial ischemia-reperfusion injury model | 30 mg·kg$^{-1}$ | Bax ↓, PI3K, p-PI3K, AKT, p-AKT, Bcl-2 ↑ | [23] |
| | Male Wistar rats (250−280 g) were subjected to ligation of the anterior descending coronary artery to establish an acute myocardial ischemia model in rats | 50−200 mg·kg$^{-1}$ | Bax ↓, Bcl-2 ↑ | [15] |
| | Male C57BL/6 mice (23.5−27.5 g), a mouse model of doxorubicin induced cardiotoxicity | 100 mg·kg$^{-1}$ | NFAT, MMP7, Fas L ↓ | [24] |
| | $H_2O_2$ induced rat bone marrow mesenchymal stem cells (rBMSCs) | 1−80 μmol·L$^{-1}$ | Caspase-3, caspase-9, Bax/Bcl-2 ↓, p-PI3K ↑ | [25] |
| | SH-SY5Y cells were induced by oxygen glucose deprivation (OGD) | 1−10 μmol·L$^{-1}$ | Bax, p53 ↓, DAPK ↑ | [26] |
| Inhibit inflammatory response | Oxygen glucose deprivation/reperfusion (OGD/R) stimulated HL-1 in mouse cardiomyocytes | 50 μmol·L$^{-1}$ | p-I$\kappa$B-$\alpha$ ↓ | [28] |
| | HG and oxLDL induced human endothelial cells (EAhy926) | 1−100 μmol·L$^{-1}$ | p-p38 MAPK, FOXO1, TXNIP, NLRP3, IL-1$\beta$ ↓ | [30] |
| Antiplatelet aggregation and anticoagulation | AA, ADP, and collagen induced platelet aggregation | 1−100 μmol·L$^{-1}$ | ERp57 ↓ | [32] |
| | AA induced platelet aggregation | 1 μmol·L$^{-1}$ | P-selectin ↓ | [33] |
| | Molecular docking; ADP induced platelet aggregation | 84−500 μg·mL$^{-1}$ | $P2Y_{12}$ ↓ | [37] |
| | Male C57BL/6 (16−20 g) high fat diet induction | 50−100 mg·kg$^{-1}$ | Cholesterol, triglyceride ↓, SR-B1, LDL-R, ABCG5, ABCG8, CYP7A1, CPT1A, p-AMPK ↑ | [39] |
| Improve endothelial dysfunction | HG and oxLDL induced human monocytic leukemia cells (THP-1) | 100 μmol·L$^{-1}$ | ABCA1, ABCG1, JAK2, p-STAT3, p-JNK, PKC, p-p38 MAPK, p-ERK1/2 ↑ | [44] |
| | LPS induced human umbilical vein endothelial cells (HUVECs) | 1-100 μmol·L$^{-1}$ | Nrf2 ↑, NLRP3 ↓ | [45] |

果, 研究者们大多采用新型药物载体 (纳米乳、脂质纳米粒、聚合物胶束、高分子微/纳米粒、接枝聚合物、脂质体) 进行迷迭香酸的药物靶向递送[50-57]。此外, 自然界中已经发现了效果更佳的迷迭香酸衍生物, 但这些尚无规律可循[58]。因此, 有针对性地对迷迭香酸进行结构修饰, 改善其生物利用度, 以提高其治疗效果, 保证其安全性, 通过临床患者试验和实验室基础研究数据相结合, 发现疗效强、无 (低) 毒性或不良反应、作用机制明确的有效单体药物, 是新药研发的重要途径。

本文围绕迷迭香酸在CVD防治中的作用途径、分子机制进行了较为系统的梳理和归纳, 以期从不同分子作用机制角度深刻认识迷迭香酸防治CVD的特点和潜力, 以期为更有效地利用迷迭香酸, 将其开发为一种新型心血管防治药物提供科学依据和理论指导。

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