

# 阿魏酸抗动脉粥样硬化的机制及进展

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**摘要:** 阿魏酸 (Ferulic Acid, FA) 是一种来源于植物次生代谢的羟基肉桂酸类酚酸, 在日常谷物中含量丰富, 具有抗氧化、抗血栓、抗炎、抗肿瘤、保护内皮细胞的功能以及保护心血管系统等多种药理学活性。目前, FA 及其衍生物已广泛应用于医药、食品添加剂等领域, 对心血管疾病的治疗有重要作用。动脉粥样硬化 (Atherosclerosis, AS) 是一种复杂的慢性炎症疾病, 是机体在脂质代谢失调、内皮细胞功能损伤的情况下, 动脉壁处发生的纤维脂肪性病变, 动脉因斑块的积聚而变硬, 造成严重的血管功能障碍。中草药当归和川芎均对 AS 有治疗效果, 而 FA 是其中的主要活性成分, 研究 FA 对 AS 的抑制作用具有非常重要的现实意义, 该研究就近年来 FA 在 AS 疾病方面的研究进展进行综述, 主要介绍了 FA 抗 AS 的几种作用方式及其潜在机制, 并从能量代谢的角度提出了 FA 激活棕色脂肪进而抑制 AS 的可能性。这将对 FA 在 AS 的预防及临床治疗中提供新的理论依据, 以期提高 FA 在日常饮食中的生物利用度, 为 FA 的进一步开发和应用提供参考。

**关键词:** 阿魏酸; 酚酸; 动脉粥样硬化; 泡沫细胞; 抗炎; 棕色脂肪

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## Mechanism and Research Advancements of the Therapeutic Activity of Ferulic Acid for Atherosclerosis

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**Abstract:** Ferulic acid (FA) is a hydroxycinnamic acid derivative of phenolic. FA originates from the secondary metabolism of plants and is prevalent in daily grains. The variety of pharmacological activities of FA include anti-oxidation, anti-thrombosis, anti-inflammation, anti-tumor, endothelial cell protection, and cardiovascular system protection. FA and its derivatives are widely used in food additives and other applications, including treatment of cardiovascular diseases, such as atherosclerosis (AS). AS is a complex and chronic inflammatory disease characterized by fibrofatty lesions in the arterial wall under the conditions of lipid metabolism disorder and endothelial cell dysfunction. AS leads to arterial hardening with the accumulation of plaques, resulting in serious vascular dysfunction. The Chinese medicinal herbs of *Angelica sinensis* and *Ligusticum sinense* Hort. have therapeutic effects on AS; FA is one of the main active components of these herbs. Therefore, studying the inhibitory effect of FA on AS is relevant and important. This article reviews recent advancements in research on the effects of FA on AS, mainly describing the various ways through which FA counteracts AS and its potential mechanisms. Additionally, from the perspective of energy metabolism, the article presents evidence suggesting the possibility that FA activation of brown fat inhibits AS. The findings summarized in this review could provide a new theoretical basis for the prevention and clinical treatment of AS with FA, suggest the increase of bioavailability of FA in daily diet, and provide a reference to further develop the therapeutic applications of FA.

**Key words:** ferulic acid; phenolic acid; atherosclerosis; foam cells; anti-inflammation; brown fat

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动脉粥样硬化 (Atherosclerosis, AS) 是一种复杂的慢性炎症疾病, AS 患者的动脉内膜有大量脂质沉积, 并在动脉内膜处形成纤维状斑块, 引起患者动脉血管壁突起硬化、血管狭窄、斑块破裂等<sup>[1]</sup>。AS 引发的动脉血管狭窄以及斑块的破裂甚至可以威胁人类的健康和生命, 同时增加心肌梗塞、心力衰竭、外周动脉疾病等心血管疾病的患病风险, 由 AS 引起的动脉粥样硬化性心血管疾病是世界范围内发病率和死亡率最高的疾病之一, 诱发 AS 的主要危险因素包括高脂血症、吸烟及高血压等<sup>[2]</sup>。AS 患者目前依赖于 3 羟甲基戊二酰辅酶 a (3-Hydroxy-3-Methyl-Glutaryl-CoA, HMG-CoA) 还原酶抑制剂、胆固醇酯转移蛋白抑制剂、胆固醇吸收抑制剂等临床药物治疗和血管重建手术<sup>[3]</sup>, 费用高昂且有不同程度的不良反应<sup>[4]</sup>。

作为一种天然存在的酚酸类物质, 阿魏酸 (Ferulic Acid, FA) 不仅是日常谷物和果蔬中最丰富的酚酸之一, 同时还是当归、川芎等治疗 AS 疾病的中草药活性成分<sup>[5]</sup>。研究表明, FA 的抗氧化和抗菌性能优于其他酚酸类物质<sup>[6]</sup>, 此外, FA 的生理特性还表现在抗血栓、抑制血小板聚集、清除血管壁的血脂沉积等方面<sup>[7]</sup>, 因此 FA 经常被当作医学热点进行研究。与一般抗 AS 疾病类药物相比, FA 的毒副作用较小、来源广泛, 具有广阔的应用前景<sup>[8]</sup>, 可以通过抗氧化、抗炎、保护血管内皮、抗纤维化、调节肠道微生物等多种方式抵抗 AS 斑块的形成<sup>[9-13]</sup>, 在抗 AS 疾病的临床应用上有极大的发展潜力。

1 阿魏酸的研究现状

阿魏酸 (4-羟基-3-甲氧基肉桂酸) 属于酚酸类化

合物, 是植物细胞壁中最丰富的羟基肉桂酸<sup>[14]</sup>, 与多糖和木质素共价连接, 有顺式和反式两种结构<sup>[15,16]</sup>。FA 具有抗氧化<sup>[17-21]</sup>、调节脂质代谢和肠道功能<sup>[22-24]</sup>、抗炎抑菌<sup>[25]</sup>、神经保护活性<sup>[26,27]</sup>、抗癌<sup>[28]</sup>、舒张血管<sup>[29]</sup>、抗血栓<sup>[30,31]</sup>等多种药理学作用, 是一种很有潜力的营养分子, 目前已被广泛地应用于食品、制药等行业<sup>[32]</sup>。此外, FA 在心血管疾病中具有很高的预防和治疗潜力<sup>[33]</sup>。近年来, FA 因其营养和药理作用而受到广泛关注, FA 已被证明具有多种抗 AS 的活性。

1.1 FA 的主要食物来源

FA 是日常谷物中含量最丰富的酚酸<sup>[34,35]</sup>, 其通常以结合或游离的形式存在于大麦、小麦、黑麦、燕麦、玉米和小米的籽粒和果皮中<sup>[36,37]</sup>, 其中大米和玉米中的主要酚类化合物也是 FA<sup>[38]</sup> (表 1)。柑橘类水果<sup>[39,40]</sup>、葡萄、香蕉、苹果中也含有 FA, 一些蔬菜如番茄、茄子、竹笋、卷心菜、菠菜和西兰花等也是 FA 的主要来源<sup>[41]</sup>。此外, FA 还存在于许多中草药中, 如阿魏、川芎、当归等。

表 1 阿魏酸在谷物中的含量

| Table 1 Content of ferulic acid in cereals |                                        |         |
|--------------------------------------------|----------------------------------------|---------|
| 谷物来源                                       | 干物质含量/( $\mu\text{mol}/100\text{ g}$ ) | 参考文献    |
| 小麦(Wheat)                                  | 317.24~349.64                          | [38]    |
| 黑麦(Rye)                                    | 463.92~603.10                          | [42]    |
| 玉米(Corn)                                   | 879.04~915.22                          | [38]    |
| 大米(Rice)                                   | 144.71~162.07                          | [38,43] |
| 燕麦(Oat)                                    | 180.05~189.27                          | [38]    |

注: 据不完全统计。

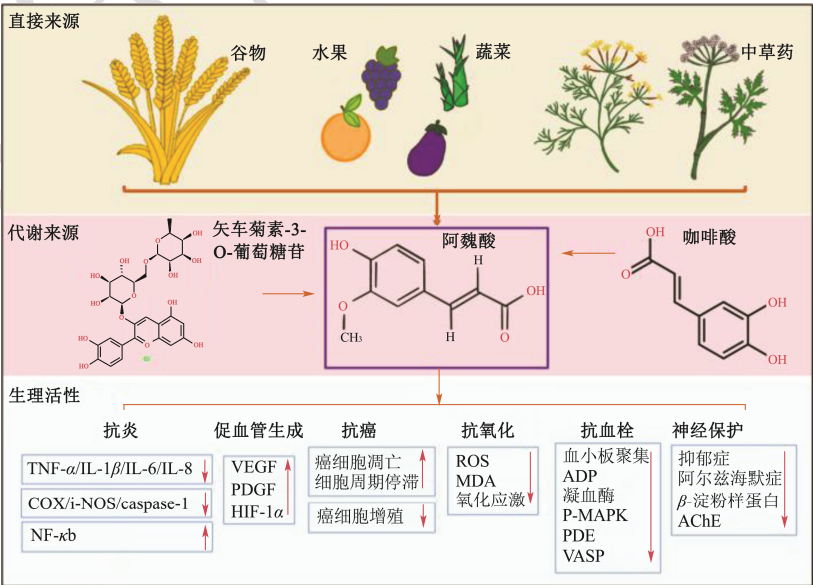


图 1 阿魏酸的来源及生理活性

Fig.1 Source and physiological activity of ferulic acid



## 1.2 FA 的代谢来源

由于 FA 在谷物中含量丰富,其在动物和人类体内的代谢也被广泛地研究。健康人体摄入添加米糠提取物的燕麦粥后,血浆中 FA 的浓度可由 84.1 nmol/L 增加到 200.2 nmol/L,提高了 2.4 倍<sup>[44]</sup>。花青素是一种对血管疾病有活性作用的多酚类物质,矢车菊素-3-O-葡萄糖苷(Cyanidin-3-Glucoside, C3G)是植物界中最多花青素,其在健康人体血清中主要代谢物是 FA 和 马尿酸<sup>[45]</sup>,在胃肠道中的酚类代谢产物包括原儿茶酸、香草酸和 FA 等<sup>[46]</sup>。咖啡酸与绿原酸也是 FA 的前体物质<sup>[47]</sup>。FA 口服后的体内主要代谢产物是硫酸阿魏酸<sup>[48]</sup>。体外研究证明,普通豆奶和酸奶中的酚类物质在上消化道的主要产物为阿魏酸酯衍生物,随后代谢为游离 FA 并由人肠道上皮细胞系 Caco-2 细胞分子层运输到内皮细胞发挥其抗炎作用<sup>[49]</sup>。

## 1.3 FA 在食品中的应用

在食品生产中,FA 主要起到食品添加剂的作用。FA 及其衍生物具有很强的抗氧化和抑菌活性,常用于食品的防腐和保鲜,在日本已作为大豆油、猪油、和亚麻籽油等食品的抗氧化剂用于生产。FA 还可用作食品交联剂生产食品和可食性食品包装膜,在提高安全性的同时还大大节约了经济成本<sup>[6]</sup>。此外,FA 在食品调味品和香料方面也有广泛的应用,诸多研究表明,FA 是制备香兰素的优良原料。FA 由于其独特的性能越来越引起了人们的关注,在食品领域中的应用也成为了研究热点。

## 2 动脉粥样硬化

### 2.1 发病过程

AS 发生的最初是由于血管壁中低密度脂蛋白(Low-Density Lipoprotein, LDL)和极低密度脂蛋白颗粒的聚积,随后积聚的 LDL 被氧化或进行其他化学修饰,高水平的循环氧化低密度脂蛋白诱导血管发生炎症反应,招募巨噬细胞吞噬脂质,形成泡沫细胞,细胞间黏附分子-1(Intercellular Adhesion Molecules 1, ICAM-1)和血管细胞黏附分子-1(Vascular Cell Adhesion Molecule 1, VCAM-1)的分泌进一步增强巨噬细胞与内皮细胞的结合,导致 AS 的发展<sup>[50-52]</sup>;肥胖导致的脂质代谢异常会促进脂肪细胞脂解,增加释放到循环中的游离脂肪酸,引发血脂异常,此时巨噬细胞黏附在内皮细胞上,更容易形成含泡沫细胞的斑块,使动脉狭窄,促进 AS 的发生<sup>[53,54]</sup>。在高血压、

高血脂等不稳定因素的作用下,AS 斑块会脱落,形成血栓,导致严重心血管疾病的发生<sup>[55]</sup>。

### 2.2 治疗现状

目前,治疗 AS 的临床药物包括 HMG-CoA 还原酶抑制剂(他汀类药物)<sup>[56]</sup>、胆固醇酯转移蛋白抑制剂<sup>[57]</sup>、胆固醇吸收抑制剂<sup>[58]</sup>等,另一方面,临床上通过血管形成术和旁路移植术等血管重建手术治疗 AS 相关的血管狭窄等病变<sup>[59]</sup>。然而仅凭药物和手术治疗不能显著改善 AS 患者的病变状况,还会产生不同程度的毒副作用。研究证明日常饮食中富含多酚的谷物、水果、蔬菜和葡萄酒等都可以缓解 AS<sup>[60]</sup>。膳食多酚可以改善脂质代谢,降低血脂水平,调节血管和内皮功能,提高机体的抗氧化性能和胆固醇清除率,调节肠道微生物群等<sup>[61]</sup>,因此通过利用日常膳食中天然存在的多酚类化合物用于开发治疗 AS 的药物是一种好的选择。

## 3 FA 对 AS 的保护作用及潜在机制

### 3.1 FA 抑制巨噬细胞泡沫化

巨噬细胞泡沫化在 AS 的发病过程中起关键作用,同时也是早期 AS 的标志性特征。在健康状态下,人体内的巨噬细胞是血浆脂蛋白代谢的主要调节剂,脂质代谢发生紊乱后,累积的胆固醇酯和经过化学修饰的 LDL,尤其是氧化的低密度脂蛋白(Oxidized Low Density Lipoprotein, Ox-LDL)被巨噬细胞摄取,形成泡沫细胞,泡沫细胞通过内皮细胞分泌的单细胞黏附分子聚集到动脉内皮,转化为斑块,造成血管狭窄。通过抑制泡沫细胞的形成可以大大减少患 AS 的概率,但目前为止还没有药物可以通过直接破坏泡沫细胞的形成来干预 AS。酚酸类物质(如 FA)的降血脂、抗氧化等特性使得其成为治疗 AS 的潜在物质,因此,研究其对泡沫细胞的抑制作用对新型药物的开发具有重要意义。

研究证明,FA 预处理可降低鼠源巨噬细胞 RAW264.7 对 Ox-LDL 的摄取,并增加腺嘌呤核苷三磷酸结合盒转运体 A1 和 G1(Adenosine Triphosphate-Binding Cassette Transporters A1 and G1, ABCA1 和 ABCG1)基因和蛋白的表达,促进胆固醇外流,减少脂质在巨噬细胞中的积累<sup>[62,63]</sup>。阿魏酸聚纳米颗粒可将人单核细胞来源的巨噬细胞表面清除受体白介素分化抗原 36、巨噬细胞清道夫受体 1 和血凝素样氧化低密度脂蛋白受体-1 的表达降低至 20%~50%,抑制其对 Ox-LDL 的摄取<sup>[64]</sup>。40 mg/(kg·d)

的 FA 通过上调腺苷酸活化蛋白激酶  $\alpha$  磷酸化以及下调固醇调节元件结合蛋白和乙酰辅酶 A 羧化酶的表达来改善脂质代谢,显著减轻载脂蛋白 E(Apolipoprotein E, ApoE) 基因敲除小鼠的 AS,其主动脉窦的病变面积可减少 1.7 倍,由高脂饮食诱导的脂肪肝损伤也大大地减轻,血脂水平也相应降低<sup>[13,65,66]</sup>。

### 3.2 FA 保护内皮细胞功能

内皮细胞是排列在血管内膜表面的一层细胞,位于动脉与血液之间,具有屏障作用,可以分泌多种细胞因子,选择性地调节血管舒张能力并参与机体的免疫反应,调节平滑肌的增殖和迁移以维持体内的动态平衡。值得注意的是,内皮细胞来源的血管细胞黏附分子可以促进单核细胞的迁移和浸润,加剧泡沫细胞在内皮的积累,导致 AS 相关心血管疾病的发生<sup>[67]</sup>。一氧化氮(Nitric oxide, NO)是内皮细胞分泌的一种重要的血管舒张调节剂,对内皮细胞具有多重保护功能,可以抑制炎症细胞因子的表达、平滑肌细胞的增殖、血小板的黏附和聚集等<sup>[68]</sup>。内皮细胞的损伤会加速血管疾病的进程,冷暴露对内皮细胞的功能会产生副作用,如增加血管收缩剂的产生并降低细胞活力等<sup>[69]</sup>。

许多研究证明了 FA 及富含阿魏酸衍生物的食品对血管具有保护作用,其发挥作用的分子途径大致包括以下几种。例如燕麦片中阿魏酸衍生物可以通过调节内皮细胞 NO 通路来保护血管功能健康,增加血管舒张因子 NO 的水平,同时降低超氧化物的水平<sup>[70]</sup>,FA 可恢复大鼠的主动脉对乙酰胆碱的正常松弛反应,通过增加 NO 的生物利用度发挥对血管内皮的保护作用<sup>[11,12]</sup>。经典的中草药当归补血汤中的有效成分 FA 对正常的斑马鱼小肠下血管具有血管生成作用<sup>[71]</sup>。在体外,FA 可诱导人脐静脉内皮细胞(Human Umbilical Vein Endothelial Cells, HUVEC)中的血管内皮生长因子(Vascular Endothelial Growth Factor, VEGF)和血小板衍生的生长因子(Platelet-Derived Growth Factors, PDGF)的表达,通过有丝分裂原激活的蛋白激酶(Mitogen-Activated Protein Kinases, MAPKs)和磷酸肌醇-3-激酶通路发挥 FA 的血管生成作用<sup>[71,72]</sup>,除此之外,FA 还可剂量依赖性地改善内皮功能障碍<sup>[73]</sup>。通过分析阿魏酸钠对 Ox-LDL 刺激的 HUVECs 基因表达谱发现,共有 32 个来自趋化因子、炎症因子、生长因子和核受体家族成员的基因被下调至正常水平,对内皮功能产生有益作用<sup>[74]</sup>。FA 可降低活化的内皮细胞中 E-选择素的表达,抑制白细胞对内皮细胞的黏附作用<sup>[75]</sup>。

血管平滑肌细胞(Vascular Smooth Muscle Cells,

VSMCs)位于血管的中间层,可以通过舒张和收缩来调节血管的压力,其过度增殖和异常迁移与 AS 的发生发展密切相关,抑制 VSMCs 的增殖可作为治疗 AS 及其相关疾病的一个潜在的治疗策略。研究表明,VSMCs 从动脉中膜向动脉内膜迁移,导致泡沫细胞的生成增加,是引发 AS 病变的主要原因。因此,抑制 VSMCs 的增殖和迁移可进一步抑制 AS 的形成。FA 还可通过抑制细胞外调节蛋白激酶和应激活化蛋白激酶(C-Jun N-terminal Kinase, JNK)的激活进一步抑制血管紧张素 II 诱导的 VSMC 增殖<sup>[76]</sup>。此外 FA 对氧化脂蛋白<sup>[77]</sup>及内皮素-1<sup>[78]</sup>诱导的 VSMC 增殖也具有相似的抑制作用。FA 还可以通过内皮一氧化氮合酶途径促进小鼠主动脉 VSMCs 产生 NO,抑制 PDGF 诱导的 VSMCs 增殖迁移<sup>[65]</sup>,缓解 AS 斑块的发展。

### 3.3 FA 通过抗氧化和抗炎作用改善 AS

氧化应激是心血管疾病的重要致病因素,它会引发机体内过氧化氢、超氧自由基、羟基自由基等自由基的水平异常增高,扰乱机体的稳态,导致各种心血管疾病如 AS 的发生。大量研究表明,饮食中加入富含抗氧化剂的活性物质可以抵抗由自由基引起的 AS。FA 具有自由基清除活性<sup>[79]</sup>,能剂量依赖性地清除超氧阴离子<sup>[80]</sup>。作为一种有效的抗氧化剂,FA 可增强抗氧化酶如超氧化物歧化酶、过氧化氢酶和谷胱甘肽过氧化物酶和对氧磷酶的活性<sup>[9]</sup>。健康人体中摄入 FA 会降低单核细胞中 NADPH 氧化酶的活性,抑制超氧化物的释放,促进细胞凋亡和坏死<sup>[81]</sup>。

AS 被视为动脉壁的一种慢性炎症疾病,而炎症是易损斑块最重要的特征之一,靶向炎症是一种治疗 AS 的有效途径。FA 是川芎、当归等中草药以及日本传统医学中常用消炎药的主要活性成分,可以通过多种方式发挥抗炎作用。富含 FA 的当归有机酸可以减轻 Ox-LDL 诱导的 HUVEC 的细胞炎症,降低黏附分子的表达水平,保护内皮细胞发挥其抗 AS 的作用<sup>[10]</sup>,中药通心络的代谢产物反式阿魏酸可以抑制巨噬细胞 THP1 中炎症因子的表达,主要是通过抑制 NOD 样受体蛋白 3(Nod-Like Receptor Protein 3, NLRP3)炎症小体通路实现的<sup>[82]</sup>。FA 的衍生物阿魏酸乙酯在体外可以通过抑制核因子  $\kappa$ B(Nuclear Factor Kappa-B, NF- $\kappa$ B)通路和激活核因子 E2 相关因子 2/血红素加氧酶 1(Nrf2/HO-1)通路,抑制肿瘤坏死因子(Tumor Necrosis Factor, TNF- $\alpha$ )和白细胞介素-1 $\beta$ (Interleukin-1 $\beta$ , IL-1 $\beta$ )细胞因子的表达,缓解脂多糖(Lipopolysaccharide, LPS)诱导的巨噬细胞炎症反应<sup>[80,83]</sup>。

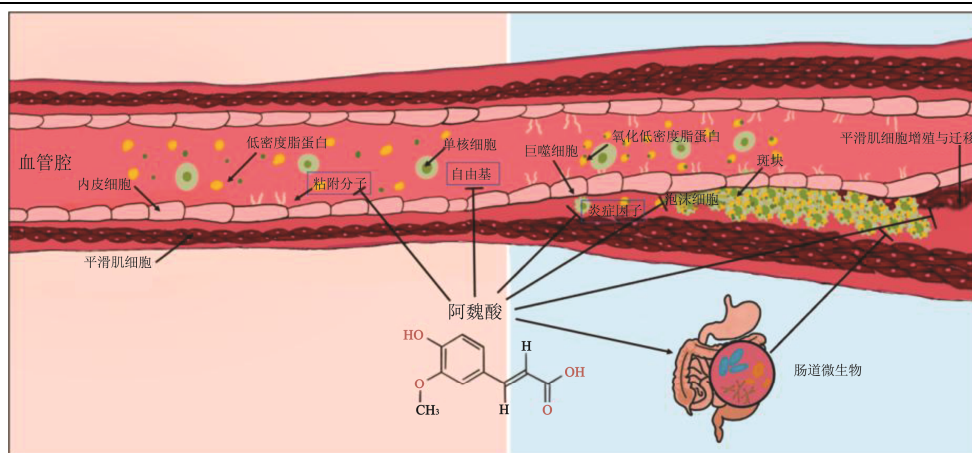


图2 阿魏酸抑制动脉粥样硬化发展的方式

Fig.2 The pathway of ferulic acid inhibits the development of Atherosclerosis

此外, FA 可以有效降低晚期糖基化终产物 (Advanced Glycation End Products, AGEs) 诱导的 HUVEC 细胞内炎症因子和黏附因子表达, 并通过 NF- $\kappa$ B/p38MAPK 信号通路减轻 AGEs 诱导的内皮细胞 HUVEC 细胞的炎症反应<sup>[84]</sup>。主要成分为 FA 的米糠酶促提取物膳食补充剂通过抑制 TNF- $\alpha$ /NF- $\kappa$ B/iNOS 信号通路来调节炎症反应<sup>[85]</sup>。另一项细胞黏附测定实验结果表明, FA 通过阻断 JNK 抑制了辐射诱导的内皮细胞黏附分子的表达<sup>[86]</sup>, 提示了 FA 可作为患者放疗的辐射防护剂, 抵抗辐射引起的炎症。大量的研究表明, FA 具有通过抑制炎症来预防和减轻 AS 的发展潜力。

### 3.4 FA 通过调肠道微生物代谢改善 AS

肠道微生物是肠道微环境的重要组成部分, 具有先天免疫调节功能, 肠道菌群在代谢失调的情况下给宿主的健康带来威胁, 诱发包括心血管疾病在内的各种疾病<sup>[87]</sup>。一些研究表明, 肠道菌群与 AS 的发展密切相关, 其在肠道屏障损伤的情况下会发生移位并诱发主动脉炎症, 对低密度脂蛋白受体基因敲除小鼠进行促炎性微生物移植可增强小鼠全身性炎症并加速 AS 的形成<sup>[88,89]</sup>。饮食来源的肠道微生物的代谢产物胆碱和磷酸胆碱产生三甲胺, 而三甲胺的代谢产物三甲胺-N-氧化物会加速 AS 的发展, 除此之外, 另外两种肠道菌群的代谢产物短链脂肪酸和 LPS 也会对 AS 斑块的稳定性会造成不同程度的影响<sup>[91,90]</sup>。

随着科学家们对肠道微生物的深入研究, 越来越多的证据表明肠道微生物可以作为 AS 的潜在治疗靶点。动物实验表明, 具有健康保护作用的天然产物可以通过调节肠道微生物的稳态来消除 AS。研究证明 FA 可以改变 *ApoE* 基因敲除小鼠肠道菌群组成中厚壁菌门和拟杆菌门的比例<sup>[92]</sup>。由 FA 作用的肠道微生物及其代

谢产物可以通过调节脂质代谢和免疫系统进而对 AS 发挥有益作用, FA 在门水平上降低了厚壁菌门 (Firmicutes) 的丰度, 增加了拟杆菌门 (Bacteroidetes) 的丰度, 科水平上降低丹毒丝菌科 (Erysipelotrichaceae) 的相对丰度, 提高瘤胃球菌科 (Ruminococcaceae) 的相对丰度。属水平上降低回肠杆菌的相对丰度, 增加了乳杆菌的相对丰度<sup>[13]</sup>, 而小米壳中提取的多酚 (主要成分包括 FA) 可以提高颤螺旋菌 (*Oscillospira*) 和 Ruminococcaceae, 最终抑制 AS 斑块的发展<sup>[94]</sup>。

治疗冠状动脉硬化的药物冠心消斑胶囊和通心络的主要成分均包括 FA, 用冠心消斑胶囊治疗小鼠后发现, 其肠道微生物群受到了影响, 小鼠肠道内的阿克曼氏菌比例增加, 通过抑制晚期糖基化终产物及其受体 (AGE-RAGE) 信号通路改善 AS 的发展, 其微生物群的变化参与了上述机制<sup>[94]</sup>。通心络可以通过改变高胆固醇饮食和球囊损伤家兔肠道菌群的结构和功能, 扭转肠道菌群的失衡, 且增加了肠道菌群相关代谢产物反式阿魏酸的丰度<sup>[9]</sup>, 改善了 AS 家兔斑块的稳定性。然而目前关于 FA 介导的肠道菌群对 AS 的调节作用的研究还不够深入, 因此对于 FA 对肠道微生物调节是否能成为有效预防 AS 的方式还需要更多针对性的科学实验来证明。

### 3.5 FA 通过激活棕色脂肪改善 AS

AS 的最大的特征是动脉内壁的脂质过度积累和内皮功能障碍, 这与脂质代谢的紊乱密不可分。目前有研究者将 AS 与棕色脂肪组织 (Brown Adipose Tissue, BAT) 开始联系起来, BAT 是一种产热组织, 激活 BAT 可降低血浆中的甘油三酯和胆固醇水平, 通过产热的方式释放能量, 并减轻 AS 的发展, 严重的 BAT 萎缩症还会加重 *ApoE* 基因敲除小鼠的 AS<sup>[95]</sup>。此外, BAT 的激活可以改善机体的糖脂代谢稳乱<sup>[11]</sup>, 抑

制炎症相关基因的表达<sup>[96]</sup>。在人体和动物中,除脑血管系统外的绝大多数动脉都被血管周围脂肪组织(Perivascular Adipose Tissue, PVAT)所包围<sup>[97]</sup>。PVAT在表型上与BAT类似。胸主动脉PVAT的基因表达与小鼠肩胛骨BAT几乎相同,人体PVAT中表达BAT特异产热蛋白解偶联蛋白1(Uncoupling Protein 1, UCP1),UCP1可将多余的能量以热量的形式耗散<sup>[98]</sup>。已有研究证明,PVAT的褐变水平与免疫细胞的浸润、促炎因子和脂肪因子的产生、AS和高血压疾病的发生呈负相关<sup>[99,100]</sup>。PVAT在血管舒张和血管收缩方面发挥重要作用,进一步提示了PVAT调节血管的功能<sup>[101]</sup>。与其他的脂肪组织相似,PVAT可以分泌脂肪细胞因子,并作用于动脉壁,AS病变的动脉周围的PVAT表现出高水平的炎症细胞因子。最近的研究证明了PVAT中的UCP1通过阻断NLRP3-IL1 $\beta$ 轴发挥抗炎的作用,从而保护血管功能,减轻AS<sup>[102]</sup>。因此,或许可以通过脂肪组织棕色化,增加能量消耗的方式来进一步抑制AS。

咖啡酸已被证明是FA的主要代谢来源,其可以通过激活 $\beta$ 3-AR/AMPK信号通路的方式促进脂肪细胞棕色化<sup>[103]</sup>。绿原酸和FA同样是咖啡酸的衍生物,其可以诱导白色脂肪细胞转化为米色脂肪细胞,增加UCP1、氧化物酶体增殖物激活的受体- $\gamma$ 共激活因子-1 $\alpha$ 的表达<sup>[104]</sup>,通过促进BAT对葡萄糖的摄取和线粒体数量及功能增加产热<sup>[105]</sup>。此外,FA的衍生物反式阿魏酸-4- $\beta$ -葡萄糖苷在冷刺激时促进小鼠BAT中UCP1的表达上调,激活BAT并增加产热<sup>[106]</sup>。我们之前的研究已表明,FA在体内的代谢来源物质C3G可作为一种酚类功能食品激活BAT,改善肥胖相关疾病,通过激活PR结构域蛋白16调控UCP1在BAT中的表达,促进BAT的产热功能并增加线粒体数量、减轻小鼠肥胖<sup>[107-109]</sup>,而FA作为一种潜在的BAT激活剂,在肥胖小鼠模型中可改善其脂质代谢<sup>[110-112]</sup>,抑制糖尿病小鼠BAT的脂质过氧化<sup>[113]</sup>。目前关于FA是否能够通过直接激活BAT的方式发挥抗AS的作用还有待研究,例如在缺乏BAT的情况下,FA是否还能减少AS斑块的聚集,在BAT存在的情况下,FA是否通过BAT改善AS的具体机制尚未解释。在之后的研究中,我们更需要进一步利用新的方法和科技手段来探究这三者之间的联系。

#### 4 提高FA生物利用度的方法

AS是世界范围内的主要死亡原因之一,膳食中天然的酚酸类物质对AS有重要抑制作用,然而活性物质由于其其在机体内的低生物利用度限制了自身对

AS的治疗作用<sup>[114-116]</sup>,因此为了进一步提高活性物质的效率及特异性,大多数研究者都致力于开发针对AS的纳米技术进行靶向治疗。Yang等<sup>[117]</sup>采用D-甘露糖修饰的硒纳米颗粒负载钙蛋白酶抑制肽,通过靶向纳米治疗的方法抑制巨噬细胞中的ABCA1和ABCG1的裂解,更有效地减轻AS。

研究者证明了10 mg/kg和14.75 mg/kg剂量的FA经大鼠口服后,生物利用度低且代谢和消除速度快,不利于FA在体内发挥其抗炎和抗氧化等作用<sup>[118]</sup>。基于FA对AS的治疗潜力和纳米技术的进步,研究者进一步探索了提高FA生物利用度的方法。对于AS进行靶向治疗可以降低药物剂量,减少不必要的副作用,还可提高其在体内的稳定性。体外试验表明,FA对泡沫细胞的抑制作用可以改善AS,但其在体内的作用受到了限制,新型的阿魏酸聚合物纳米颗粒可有效抑制巨噬细胞对Ox-LDL的摄取以及活性氧(Reactive Oxygen, ROS)的生成量,FA通过己二酸或二羟基乙酸连接剂<sup>[64]</sup>,在聚酸酐酯内进行化学共轭,保护FA的稳定性,并在可控的条件下释放FA,发挥其最大效率。将热敏壳聚糖水凝胶作为FA的载体,对其进行体内和体外模型实验,FA-凝胶处理可通过降低内源性ROS生成,并改善小鼠的炎症水平和纤维化区域<sup>[119]</sup>。

对比来看,上述FA聚合物纳米颗粒中将FA聚酸酐酯进行化学共轭的方法可以避免羧酸发生脱羧反应<sup>[64]</sup>,使FA在体内的稳定性进一步提高,同时可以增加FA在聚合物中的总质量。此外,这种纳米颗粒具有很强的生物降解能力,实现了FA在体内的可控释放,使其充分地发挥自身生物活性,更精准地靶向抑制泡沫细胞的形成。而热敏壳聚糖水凝胶具有抑菌性以及良好的生物相容性,将其作为FA的递送载体,可达到FA持续释放的效果,缓释时间可达28 d<sup>[119]</sup>,且对人体组织没有毒害作用。总的来说,采用靶向新型聚酸酐酯纳米颗粒载体技术和热敏壳聚糖水凝胶均可提高FA在体内的释放率,解决了FA应用的主要限制。但目前关于提高FA生物利用度的方法研究较少,未来还需进一步探索和研究,寻找其他提高FA生物利用度的方法。

#### 5 总结与展望

FA是日常谷物和水果蔬菜中主要的羟基肉桂酸,大量的文献数据表明FA可以抑制AS疾病的发生与发展,本文通过对相关研究的检索,总结了FA对AS发挥作用的相关机制。FA可通过促进胆固醇外流,减少脂质在巨噬细胞中的积累进而抑制巨噬细胞的泡沫化;FA还可通过调节NO等血管生成因子来改善内皮

细胞功能,并抑制 VSMCs 的增殖和迁移,降低 AS 斑块的发生率;FA 的抗炎和抗氧化活性使 AS 的病变程度大大降低;FA 还可通过调节肠道菌群的方式发挥对 AS 的改善作用。因此,通过膳食干预补充富含 FA 的食物在一定程度上可提高机体自身抗炎、抗氧化能力,改善内皮功能与脂质代谢水平,有助于 AS 患者的健康。

然而目前以下方面的研究仍有待进一步开展。首先,在 FA 抗 AS 的有效途径方面,有关 FA 能否通过激活 BAT 的方式抑制 AS 还需要进一步的研究确定,可以结合 BAT 特异性基因敲除和过表达的手段进行相关的动物实验。其次,目前关于 FA 抗 AS 在临床效果上的试验研究较少,也有待进一步探索。最后,提高 FA 体内生物利用率的方法还需要一定的研究进行补充。这些针对性的研究为深度利用富含 FA 的食品资源提供了理论依据,也为 AS 等特殊人群精准开发营养健康食品具有重要意义,为健康中国 2030 战略的实现具有实际的意义。

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