# 白藜芦醇调节脂质代谢研究进展

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**摘要** 能量摄入与能量消耗失衡引起脂肪组织增多及脂质代谢紊乱，继而引发肥胖、糖尿病、心血管疾病等代谢类疾病。白藜芦醇(RSV)是一种天然的芪类多酚化合物，可以通过调节脂合成及氧化分解、脂肪因子的分泌、脂肪组织的产热及抑制炎症有效改善肥胖等代谢类疾病。目前，RSV 调节脂质代谢的研究受到广泛关注，并取得很大进展。本文综述近年来 RSV 调节脂质代谢的研究，为 RSV 改善代谢类疾病方面的应用研究提供理论参考。

**关键词** 白藜芦醇；代谢物；脂代谢；作用机制
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随着人们生活方式和饮食习惯的变化，肥胖等代谢类疾病已成为日益严重的公共卫生问题[1]。世界卫生组织的数据表明，2016 年全球成年人中肥胖个体数超过 6.5 亿，占比为 13%。肥胖个体因体内脂肪长期过多，能量平衡遭到破坏而导致血糖、血脂及蛋白质代谢出现紊乱，引发慢性低度炎症、心血管疾病及其它多种生理病理障碍[2]。目前治疗肥胖的主流手段有药物干预、饮食控制及减肥手术，然而这些方法具有不持久、易反弹及副作用大等缺点。近年研究表明白藜芦醇(RSV)等天然产物对肥胖具有改善功能，且副作用小，是安全有效的治疗手段。

RSV 属于芪类的多酚化合物，1940 年首次发现于白藜芦根部，是植物在应激条件下产生的抗毒素，主要以糖苷的形式存在于葡萄、虎杖、花生、蓝莓、桑树等植物的根茎、叶子及果实中[3]。目前在保健品、化妆品领域已广泛应用。近年来，大量试验研究表明 RSV 可以通过调节脂合成及氧化分解、脂肪因子的分泌、脂肪组织的产热及抑制炎症改善肥胖。由于 RSV 的安全性和高效性，其在预防肥胖研究领域成为热点。本文以 RSV 调节脂质代谢为切入点，对 RSV 的性质、代谢、作用机理等方面进行总结，旨在为 RSV 在改善肥胖等代谢类疾病方面的应用研究提供理论参考。

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## 1 白藜芦醇

RSV 的化学名为 3,4′,5-三羟基二苯基乙烯，是一种芪类多酚化合物，分子式为 $C_{14}H_{12}O_3$，分子质量为 228.25 g/mol，结构式如图 1 所示，其纯品为针状无色结晶，熔点为 256~258 ℃，难溶于水，易溶于丙酮、乙醇等有机溶剂[4]。天然的 RSV 有顺式和反式两种构象，此外，RSV 还可与葡萄糖结合生成顺式和反式的糖苷，与顺式结构相比，反式结构更加稳定，且生物活性更强[5]。

RSV 是植物在真菌感染、紫外线辐射等胁迫条件下产生的抗毒素，广泛分布于葡萄、花生、虎杖等多种植物中。常见植物中 RSV 含量见表 1，其中，毛茛科芍药属紫牡丹种子中 RSV 含量最高，为 870 μg/g[6]。目前，获取 RSV 的手段主要有植物提取，化学合成及生物合成 3 种。由于植物提取得率低，化学合成能耗高且污染环境，因此通过生物合成获取 RSV 是非常有前景的方向[7]。

## 2 白藜芦醇在机体中的代谢与分布

RSV 的生物活性，如减肥、改善心脑血管疾病、改善糖尿病等，然而，它的生物利用度不足 1%，在血液中的浓度很低，其低生物利用度和高生物活性之间存在明显矛盾。Boocock 等[11]给健康志愿者单次口服 0.5·5 g RSV，在 0.8~1.5 h 内出现最大血药浓度，仅为 0.3 ~2.4 μmol/L。Kapetanovic 等[12]给大鼠连续 14 d 灌胃 150 mg/kg/d 的 RSV，血液中 RSV 的最大浓度为 2.2 μmol/L。然而，在体外的细胞实验中，RSV 发挥作用的浓度范围可以高达 5~50 μmol/L[13-14]。为解释低生物利

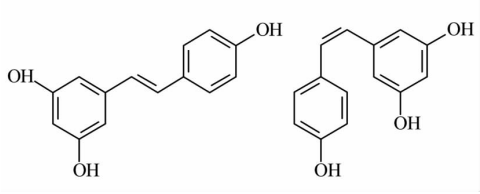

**图 1　白藜芦醇的反式(左)及顺式(右)结构**

Fig.1　The chemicals tructure of trans-resveratrol(left) and cis-resveratrol(right)

**表 1　植物中白藜芦醇含量[4,8-10]**

Table 1　Resveratrol content in certain natural plants[4,8-10]

| 植物种类 | 含量 |
|---|---|
| 花生 | 0.125~1.626 μg/g |
| 虎杖 | 0.42~0.63 mg/g |
| 葡萄 | 0.16~3.54 μg/g |
| 牡丹 | ~0.87 mg/g |
| 开心果 | 0.09~1.67 μg/g |
| 蔓越莓 | 0.24~0.36 μg/g |
| 桑葚 | 3.70~3.82 μg/g |

用度和高生物活性之间的矛盾,研究 RSV 的代谢与分布是非常必要的。

RSV 在体内的代谢包括Ⅱ相代谢和肠道菌群代谢。首先,RSV 进入体内经胃到达小肠后,主要以被动扩散的方式被肠上皮细胞吸收[15]。75% RSV 进入肠上皮细胞后,在尿苷 5′-二磷酸葡萄糖醛酸转移酶 (5′ -diphospho-glucuronosyltransferases, UGTs)和磺基转移酶(sulfotransferases,SULTs)的作用下发生Ⅱ相代谢, 转化为葡萄糖醛酸苷和硫酸盐[16]。然后,RSV 及其代谢物通过肠上皮细胞顶膜和底膜的转运蛋白[17],如乳腺癌耐药蛋白(breast cancer resistance protein,BCRP/ABG2)、多药耐药相关蛋白 2 (multidrug resistance-associated protein 2,MRP2/ABC2)及多药耐药相关蛋白 3(multidrug resistance -associated protein 3,MRP3/ABC3) 等, 进入肠腔或门静脉毛细血管。这时,RSV 及其代谢物的走向分为两部分: 一部分经肠腔进入大肠后,继续被肠道菌群代谢[18],菌群代谢物能透过肠壁进入体循环;另一部分到达血液后,与血液中的蛋白质如脂蛋白[19]、血红蛋白和白蛋白[20]结合经门静脉进入肝脏后参与肝肠循环,进而到达肾及其它外周组织。最后,RSV 及代谢物通过尿液和粪便排出体外,约占摄入的 75%[21-22]。

RSV 在体内的代谢物分为机体代谢物和肠道菌群代谢物。机体代谢物主要有白藜芦醇葡萄糖醛酸苷(RSV-glucuronide,RSV-G)和白藜芦醇硫酸盐(RSV-sulfate,RSV-S)。目前检测到的 RSV-G 及 RSV-S 最多有 16 种[23],如:RSV-3-O-硫酸盐(RSV-3-O-sulfate,RSV-3-S)、RSV-4'-O-硫酸盐(RSV-4′O-sulfate,RSV-4'-S)、RSV-3-O-葡萄糖醛酸苷 (RSV-3-O-glucuronide,RSV-3-G)、RSV-4-O-葡萄糖醛酸苷 (RSV-4'-O-glucuronide,RSV-4'-G)、RSV 双硫酸盐(RSV-3,4'-O-disulfate,RSV-diS) 及 RSV 磺基葡萄糖醛酸苷(RSV-sulfoglucuronide,RSV-S-G)等。它们主要分布在肝脏、肾脏及胃肠道中,这可归因于这些器官中代谢 RSV 产生 RSV-G 及 RSV-S 的酶的基因表达量高[24]。肠道菌群代谢物主要有二氢白藜芦醇 (dihydro-resveratrol DHR)、3,4'-二羟基-反式-二苯基乙烯和半月薹酚(lunularin LUN)等[18]。与 RSV 类似,DHR 和 LUN 也可以被代谢为葡萄糖醛酸苷和硫酸盐,如:DHR-硫酸盐(DHR-sulfate,DHR-S)、DHR-葡萄糖醛酸苷 (DHR-glucuronide,DHR-G)、DHR-双葡萄糖醛酸苷(DHR-diglucuronide,DHR-diG)、DHR-磺基葡萄糖醛酸苷(DHR-sulfoglucuronide,DHR-S-G)、LUN-硫酸盐(LUN- sulfate,LUN-S)及 LUN-葡萄糖醛酸苷(LUN-glucuronide,LUN-G)。DHR、LUN 及其葡萄糖醛酸苷、硫酸盐不仅分布在结肠,还在血清、胆汁、肾脏和肝脏中被检测到,并且它们的含量明显高于 RSV 及 RSV-S、RSV-G[25]。本文选取近十年关于 RSV 及其代谢物在体内分布及含量的代表性研究(表 2)。除了以上 RSV 的代谢物外,随着检测技术的进步, 研究者在动物的粪便和尿液中检测到新的 RSV 代谢物。2019 年 Wang 等[26]在小鼠粪便中检测到 4-羟基苯丙酸、4-羟基苯乙酸、3-羟基苯甲酸及 3-羟基苯丙酸。2020 年 Liu 等[23]在大鼠尿液及粪便中检测到 4-羟基苯甲酸。在肠道菌群代谢其它多酚的研究中也检测到羟基苯乙酸、羟基苯丙酸等酚酸[27]。近 3 年的研究表明这些酚酸与多酚的生物活性有关[28-29]。有关 RSV 酚酸类代谢物的药代动力学研究对于解释 RSV 的生物活性非常重要。目前,这方面的研究较为缺乏。

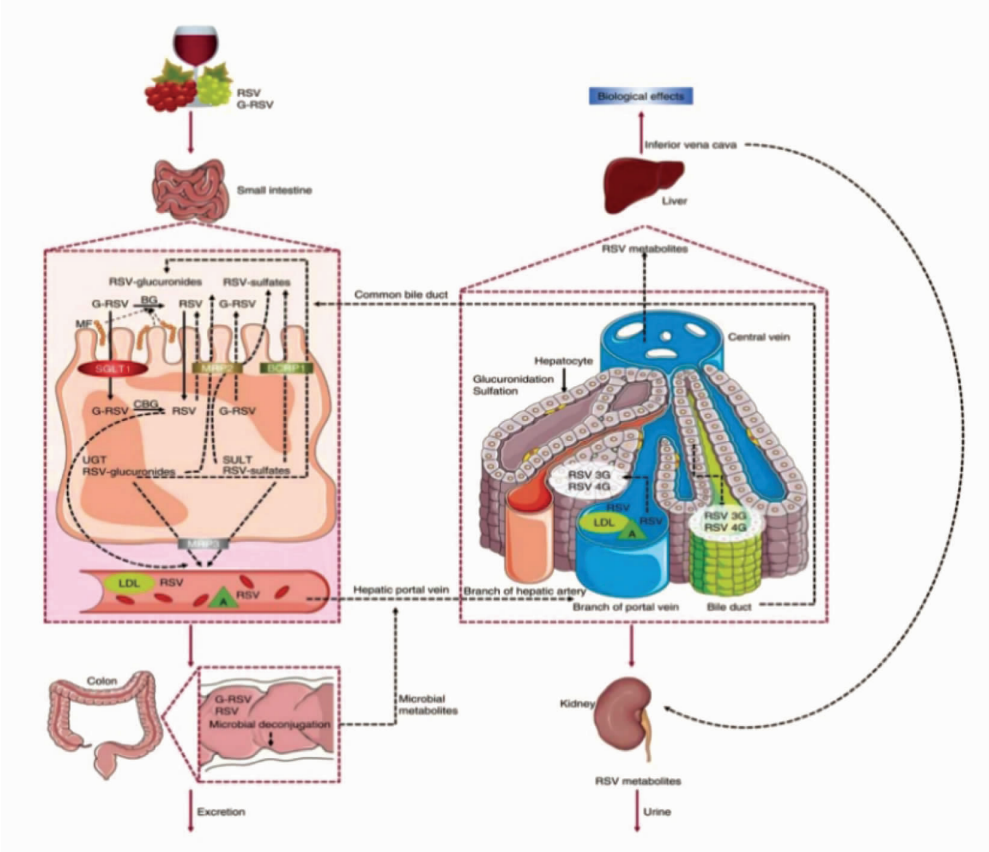


**图 2 白藜芦醇的吸收与代谢[25]**

Fig.2 Absorption and metabolism of resveratrol[25]

## 3 白藜芦醇调节脂代谢的作用机制

2006 年,Lagouge 等[39]的研究首次表明 RSV 对肥胖有改善作用。截至目前,关于 RSV 改善代谢类疾病的研究取得很大进展,近 15 年相关代表性研究如表 3 所示[40-42]。体外和体内研究表明 RSV 改善肥胖的作用机理主要体现在调节脂代谢及脂肪因子分泌、刺激机体产热、抗炎及调节肠道菌群 4 个方面。

### 3.1 调节脂代谢及脂肪因子分泌

脂代谢主要包括甘油、脂肪酸、磷脂、胆固醇及血浆脂蛋白等代谢过程[43]。RSV 通过促进脂肪酸 $\beta$ 氧化[44],抑制脂肪酸及脂肪合成[45],减少体内脂肪聚集,改善肥胖。体外实验中,Huang 等[46]发现 RSV 通过激活过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor,PPAR$\alpha$ 及 PPAR$\gamma$),抑制巨噬细胞脂肪酸转运蛋白 1(fatty acid transport protein 1,FATP1)的基因表达,进而减少自由脂肪酸摄入及甘油三酯聚集。体内实验中,Wang 等[47]研究表明补充 RSV 抑制了肥胖小鼠附睾脂肪中脂合成相关酶,如:脂肪酸合成酶(fatty acid synthase,FAS)、硬脂酰辅酶 A 去饱和酶 1(Stearoyl-CoA desaturase 1,SCD1)的基因表达,促进了脂肪氧化相关酶,如:肉毒碱棕榈酸酰基转移酶 1A(carnitine palmitoyl transferase 1A,CPT1A)及中链乙酰辅酶 A 脱氢酶(mediumchain Acyl-CoA dehydrogenase,MCAD)的基因表达,增强了脂肪氧化并抑制脂肪合成,进而改善小鼠肥胖。同时,临床试验结果表明 RSV 能影响脂代谢。例如,Timmers 等[40]选取 11 名肥胖患者进行随机双盲试验,持续 30 d 给干预组补充 150 mg/d RSV,结果显示 RSV 激活肌肉中 AMPK/SIRT1/PGC-1$\alpha$ 通路,改善了肌肉线粒体以脂肪酸为底物的呼吸作用,降低了血液中甘油三酯及炎症因子水平。Jorge 等[48]给 13 名肥胖患者连续 3 个月补充 250 mg/d 的 RSV,并辅助适当的锻炼,结果表明 RSV 提高了血液中总胆固醇、高密度脂蛋白胆固醇、极低密度脂蛋白胆固醇及尿素的含量。

关于 RSV 调控脂代谢机制的研究中,目前较

**表 2　白藜芦醇及其代谢物在体内分布研究**

Table 2　Study on the distribution of resveratrol and its metabolites *in vivo*

| 样本 | 样本来源 | 补充方式 | RSV 代谢物 | 参考文献 |
|---|---|---|---|---|
| 血液、尿液、粪便 | 大鼠($n$=18) | 单次静脉注射,15 mg/kg | RSV、RSV-S、RSV-G | [30] |
| | 猪($n$=5) | 单次灌胃,5.9 mg/kg BW | RSV、cis-RSV、RSV-diG、RSV-S、RSV-triS、RSV-3-G、RSV-S、DHR-3-G、DHR-S | [31] |
| | 人($n$=23) | 单次补充 250 mgRSV 或 250 mgRSV 与 20 mg 胡椒碱 | RSV、RSV-3-G、RSV-4'-G、RSV-3-S | [32] |
| | 大鼠($n$=10) | 5、25 mg/kg/d,持续 22 周 | RSV、RSV-3-S、RSV-3-G | [33] |
| | 小鼠($n$=3~20) | 单次灌胃 150 mg/kg;40 mg/kg/d 添加于饲料,持续 3 个月 | RSV、RSV-3-G、RSV-4'-G、RSV-diG、RSV-S-G、RSV-3-S、DHR、DHR-3-S、DHR-4'-S、DHR-3-G、DHR-4'-G、DHR-S-G | [34] |
| | 小鼠($n$=3) | 单次灌胃 10 mg/kg | RSV、RSV-3-G、RSV-3-S、RSV-3,4'-diS | [24] |
| | 人($n$=10) | 单次补充 200 mg | RSV、RSV-3-G、RSV-4'-G、RSV-3-S、RSV-3,5-diG、RSV-3,4'-diG、RSV-3-S-G、RSV-4'-S-G、DHR、DHR-G、DHR-S、DHR-S-G | [35] |
| | 小鼠($n$=10) | 饲料添加 0.05%(质量分数),持续 4 周 | RSV、RSV-S、RSV-G、RSV-S-G、DHR、DHR-S、DHR-S、DHR-diG、DHR-S-G、LUN、LUN-S、LUN-G | [25] |
| | 人($n$=59) | 每天饮用 252 mL 葡萄酒或去酒精葡萄酒,持续 4 周 | RSV-3-G、RSV-4'-G、cis-RSV-3-G、cis-RSV-4'-G、RSV-4'-S、RSV-3-S、cis-RSV-4'-S、cis-RSV-3-S、RSV-S-G、RSV-3,4'-diS、DHR、DHR-G1、DHR-G2、DHR-S1、DHR-S2、DHR-S-G | [36] |
| 五脏、眼睛、胃肠道 | 大鼠($n$=6) | 单次补充 2、4 mg/kg 虎杖根提取物 | RSV、RSV-G、RSV-S-G | [37] |
| | 小鼠($n$=3~20) | 单次灌胃 150 mg/kg、40 mg/kg/d 添加于饲料,持续 3 个月 | RSV、RSV-3-G、RSV-4'-G、RSV-diG、RSV-S-G、RSV-3-S、DHR、DHR-3-S、DHR-4'-S、DHR-3-G、DHR-4'-G、DHR-S-G | [34] |
| | 小鼠($n$=3) | 单次灌胃 10 mg/kg | RSV、RSV-3-G、RSV-3-S、RSV-3,4'-diS | [24] |
| | 小鼠($n$=10) | 饲料添加 0.05%(质量分数),持续 4 周 | RSV、RSV-S、RSV-G、RSV-S-G、DHR、DHR-S、DHR-diG、DHR-S-G、LUN、LUN-S、LUN-G | [25] |
| | 人($n$=35) | 补充 3 次,每次 100 mg | RSV、RSV-3-G、RSV-4'-G、RSV-3-S | [38] |

注：表中的 RSV 均为反式白藜芦醇,cis-RSV 均为顺式白藜芦醇,RSV-triS 为白藜芦醇-三硫酸盐,RSV-diG 为白藜芦醇-二葡萄糖醛酸苷,RSV-3,5-diG 为白藜芦醇-3,5-二葡萄糖醛酸苷,RSV-3,4′-diG 为白藜芦醇-3,4′-二葡萄糖醛酸苷,RSV-3-S-G 为白藜芦醇-3-硫酸基葡萄糖醛酸苷,RSV-4′-S-G 为白藜芦醇-4′-硫酸基葡萄糖醛酸苷,DHR-3-S 为二氢白藜芦醇-3-硫酸盐,DHR-4′-S 为二氢白藜芦醇-4′-硫酸盐,DHR-4′-G 为二氢白藜芦醇-4′-葡萄糖醛酸苷,DHR-G1 为二氢白藜芦醇-葡萄糖醛酸苷-1,DHR-G2 为二氢白藜芦醇-葡萄糖醛酸苷-2,DHR-S1 为二氢白藜芦醇-硫酸盐-1,DHR-S2 为二氢白藜芦醇-硫酸盐-2。

**表3 白藜芦醇改善肥胖的机制研究**

Table 3 Study on the mechanism of resveratrol improving obesity

| 研究对象 | 个体数 | 干预方式 | 效果 | 参考文献 |
|---|---|---|---|---|
| 斑马鱼 | 58~121 | 20 μmol/L,8 周,饮水获取 | 激活 AMPK/SIRT1/PPARγ 通路,调节脂代谢 | [49] |
| 小鼠 | 5 | 400 mg/kg/d,30 d,灌胃 | 激活 SIRT1 表达,脱乙酰化 ATF6,减少脂滴聚集,改善肝脂肪变性 | [44] |
| | 7 | 300 mg/kg BW/d,60 d,饲料添加 | 降低胆固醇含量及脂肪组织中 *PPARγ*、*SREBP-1C*、*ACC*、*FAS* 等脂合成基因表达 | [45] |
| | 10 | 300 mg/kg/d,16 周,灌胃 | 降低脂肪合成酶 FAS、SCD1 表达,增加脂肪氧化酶 CPT1A、MCAD 表达 | [47] |
| | 10 | 0.4%,16 周,饲料添加 | 降低 miR-107 和 miR-10b 表达,增加 PPARγ 及 CPT1A 表达,抑制脂合成 | [50] |
| | 6 | 276 或 400 mg/kg 饲料,9 周,饲料添加 | 降低肝脏 m6A 甲基化水平并上调 *PPARα* 基因表达,改善脂代谢紊乱 | [52] |
| | 8 | 400 mg/kg,8 周,饲料添加 | 增加皮下脂肪中 SIRT1 及 FNDC5 表达,刺激产热基因表达 | [62] |
| | 10 | 2 或 4 g/kgdiet,12 周,饲料添加 | 激活附睾脂肪 Sirt1 表达, 增加棕色化蛋白 PRDM16 及棕色化基因 *TMEM26* 和 *CIDEA* 的表达 | [70] |
| | 10 | 200 或 400 mg/kg/d,18 周,饲料添加 | 增加 WAT 中 *CCR2* 基因表达,缓解炎症及巨噬细胞浸润,改善肥胖 | [83] |
| | 7 | 0.4%RSV,8 周,饲料添加 | RSV 刺激腹膜脂肪中 Sirt1 蛋白表达,增加了 PGC-1α,PPARγ,UCP1 的蛋白量,FMT 证明肠道菌群参与其中 | [87] |
| 大鼠 | 10 | 100 mg/kg BW/d,8 周,灌胃 | 激活 PKA/AMPK/PPARα 通路,改善肝脂肪变性 | [46] |
| | 10 | 500 或 100 mg/kg BW/d,6 周,灌胃 | 降低了结肠 *CB1* 及 *CB2* 基因表达,上调紧密连接蛋白基因表达,改善肠屏障完整性及炎症。 | [81] |
| | 6~7 | 30 mg/kg BW/d,30 d,饲料添加 | RSV 降低了瘦素,增加了下丘脑 p-STAT3 含量,改善瘦素抵抗 | [58] |
| 人群 | 11 | 150 mg/d,30 d | 降低了休息睡眠时的代谢率,激活 AMPK/Sirt1/PGC-1α,降低了 ALT,IL-6,TNF-α | [40] |
| | 11 | 150 mg/d,30 d | 下调了 Wnt,Notch 通路,促进脂生成,减小脂肪细胞面积 | [90] |
| | 66~74 | 1 000 或 150 mg/d,16 周 | 低剂量对代谢综合征没有改善效果, 高剂量增加了血液总胆固醇和低密度脂蛋白胆固醇含量 | [91] |
| | 20 | 150 mg/d,6 个月 | RSV 降低了血液中糖化血红蛋白 HbA1c 含量,对胰岛素敏感性没有影响 | [91] |
| | 12 | 250 mg/d,3 个月 | 增加了血液中总胆固醇,HDL-c,VLDL-c 含量,对代谢综合征有益 | [48] |

注:ATF6 为活化转录因子 6,FMT 为粪菌移植,CB1 为内源性大麻素受体 1,CB2 为内源性大麻素受体 2,ALT 为谷丙转氨酶,HDL-c 为高密度脂蛋白胆固醇,VLDL-c 为极低密度脂蛋白胆固醇。

为成熟的作用通路是腺苷酸活化蛋白激酶(AMP activated protein kinase,AMPK)/脱乙酰化酶 1(sirtuin-1,SIRT1)通路[44,46]。Ran 等[49]发现,在斑马鱼中 RSV 通过 AMPK/SIRT1/PPARγ 通路调节脂代谢,进而降低了血液总胆固醇和甘油三酯含量,减轻体重。随着表观遗传学研究的深入,研究者们发现 miRNA[50-51]、m6A 甲基化[52]及去甲基化核因子 E2 相关因子 2(nuclearfactor erythroid 2 related-factor 2,Nrf2)信号[53]等表观遗传修饰也参与了脂代谢调控,抑制脂质聚集。在高糖处理的 HepG2 细胞中,RSV 降低了 miR-107 和 miR-10b 表达,增加了 *PPARγ* 及 *CPT-1a* 基因表达,抑制脂合成并改善肝脂肪变性[50]。Wu 等[52]的研究表明 RSV 降低了肥胖小鼠肝脏中 m6A 甲基化水平,增加 *PPARα* 基因表达,进而改善脂代谢紊乱。同时,生物钟基因 *Bmal1* 的激活[54]及线粒体三磷酸腺苷酶家族蛋白 3(ATPase family AAA domain-containing protein,ATA3)[55] 也参与了 RSV 改善脂代谢。在脂肪酸诱导的脂肪变性 HepG2 细胞中,RSV 通过增加 *Bmal1* 基因表达降低 FAS 及固醇调解原件结合蛋白-1C(sterol regulatory element binding protein-1C,SREBP-1C)的表达,恢复了脂代谢紊乱。

脂肪因子是脂肪组织分泌的一类蛋白质,以自分泌或旁分泌的方式维持能量代谢稳态。常见的脂肪因子有:瘦素、脂连素、抵抗素、成纤维细胞生长因子-21(fibroblast growth factor 21,FGF21)及纤连蛋白域包含蛋白 5(fibronectin domain contains protein 5,FNDC5)等[56]。RSV 改善肥胖与脂肪因子有关,一方面,RSV 能改善肥胖引起的瘦素抵抗;另一方面,RSV 通过增加 FGF21 和 FNDC5 的含量调节脂代谢,刺激机体产热,进而改善肥胖。瘦素抵抗是指在肥胖状态下,血液中瘦素含量增加,受体敏感性下降,无法发挥抑制食欲及刺激能量消耗的作用[57]。研究表明,RSV 不仅通过增加磷酸化信号传导子及转录激活子 3(phosphorylated signal transducer and activator of transcription-3,p-STAT3)含量改善下丘脑瘦素抵抗[58],还通过增加肝脏[59]和肌肉[60]中瘦素受体含量,降低脂肪组织内质网应激[60],改善周围组织的瘦素抵抗。Li 等[61]给肥胖小鼠补充 RSV 后激活肝脏中 SIRT1 表达,上调 FGF21 含量,进而增加脂肪酸氧化基因表达,减轻体重。Andrade 等[62]的研究表明 RSV 通过激活肥胖小鼠皮下脂肪的 SIRT1,促进 FNDC5 含量增加,上调脂肪产热基因表达,促进机体产热并改善肥胖。

### 3.2　刺激机体产热

哺乳动物的棕色脂肪组织(brown adipose tissue,BAT)含有大量的线粒体及解偶联蛋白 1(un-coupling protein 1,UCP1)[63],能消耗多余的热量,减轻体重。白色脂肪组织(white adipose tissue,WAT)中线粒体含量较少,当 WAT 细胞合成更多线粒体及表达 UCP1 时,其产热量增加,该过程称为 WAT 棕色化[64]。除了低温、运动等外部刺激外,RSV 等多酚类物质也能刺激 BAT 产热及诱导 WAT 棕色化[65]。Wang 等[66]发现在体外腹股沟白色脂肪细胞和肥胖小鼠 BAT[67]中,RSV 能上调 PR 结构域 16(PR domain containing 16,PRDM16)、UCP1、过氧化物酶体增殖物激活受体 γ 辅激活因子 1α(peroxisome proliferator-activated receptor-r-coactivator 1α,PGC1α)等棕色脂肪标志物来诱导 WAT 棕色化,降低 WAT 质量,缓解肥胖。Serrano 等[68]的研究表明,在哺乳期给小鼠补充 RSV,成年后其 WAT 中棕色化基因 *Slc27a1* 及 *Prdm16* 表达高于对照组。目前,关于 RSV 刺激 BAT 产热及诱导 WAT 棕色化的机理方面,研究较多的是 AMPK/SIRT1/PGC1α 通路[62,69]。研究者主要采用抑制剂[67]及 RNA 干扰[69]验证 AMPK 和 SIRT1 在该通路中的作用。Li 等[70]的研究表明 RSV 刺激肥胖小鼠棕色化基因表达与 Sirt1 有关,当采用腺病毒载体表达 shRNA 手段抑制 Sirt1 蛋白表达后,附睾脂肪中棕色化蛋白 PRDM16 及棕色化基因 *TMEM26* 和 *CIDEA* 的表达上调消失。同时,哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)[71]及石胆酸[72]也与 RSV 刺激机体产热有关。体外试验表明,RSV 通过激活 mTOR 诱导 3T3L1 脂肪细胞棕色化[71]。在 db/db 小鼠中,RSV 处理增加了血液及粪便中石胆酸含量,石胆酸激活受体 G 蛋白胆汁酸偶联受体 5(Takeda G protein-coupled receptor 5,TGR5),进而上调 UCP1 蛋白表达激活 BAT 并促进 WAT 棕色化,提高肥胖小鼠的葡萄糖稳态[72]。此外,Serrano 等[73]发

现 RSV 刺激 WAT 棕色化与性别有关，在生命早期补充 RSV 能增加成年雄鼠的 WAT 棕色化，而对雌鼠没有效果。

### 3.3 抗炎作用

肥胖的发生过程中伴随着长期的低度炎症[74]。肥胖状态下肠屏障功能受损，革兰氏阴性菌产生的脂多糖透过破损肠屏障进入体循环，进而激活免疫系统释放炎性细胞因子，引起系统性慢性炎症[75]。许多研究表明 RSV 具有抗炎作用[76]。在体外培养的脂肪细胞中，RSV 抑制炎症因子白介素 6(interleukin-6，IL-6)、白介素 8(interleukin-8，IL-8)及单核细胞趋化蛋白 1(monocyte chemoattractant protein-1，MCP-1)的表达[77]。在动物模型中，Jimenez 等[78]发现 RSV 降低了恒河猴白色脂肪组织中核因子 κB (nuclear factor kappa-B，NF-κB)的磷酸化水平，进而抑制了炎症因子肿瘤坏死因子 α(tumor necrosis factor-α，TNF-α)、IL-6、白介素 1β(interleukin-1β，IL-1β)及脂连素的表达。目前的研究表明 RSV 抗炎的机理主要有改善肠屏障和内质网应激。一方面，RSV 能上调肠道表面紧密连接蛋白(Occludin)、密封蛋白(Claudin)、胞质紧密粘连蛋白 1 (zonula occludens-1，ZO-1)[79]和肠道黏液中上皮细胞膜结合黏液素(mucin，MUC)、肠三叶因子 3 (intestinal trefoil factor，TFF3)[80]的表达，改善肠道物理屏障和化学屏障完整性，减轻机体的内毒素血症及炎症反应，改善小鼠的胰岛素抵抗及相关代谢类疾病。同时，RSV 改善肠屏障完整性与内源性大麻素系统有关，Chen 等[81]的研究表明给肥胖大鼠补充 RSV，降低了肠道中大麻素受体 1 的 mRNA 水平，进而增加了肠道紧密连接蛋白的基因表达，改善了非酒精性脂肪肝。此外，RSV 通过抑制脂肪组织中 SIRT1[82]及 CC 趋化因子受体 2 (CC chemokine receptor type 2，CCR2)[83]表达缓解内质网应激及巨噬细胞浸润，减轻炎症。Ding 等[83]发现 RSV 显著降低了肥胖小鼠内脏脂肪中 CCR2 及炎症因子 MCP-1、TNF-α 和 IL-6 的基因表达，减少巨噬细胞浸润和炎症反应，最终改善糖代谢及肥胖。

### 3.4 调节肠道菌群

肠道菌群作为人体的虚拟器官，不仅与肥胖、糖尿病、心血管疾病等多种代谢类疾病相关，而且是治疗这些疾病的重要靶点[84]。RSV 作为益生元，与肠道菌群互相作用，改善肥胖。一方面，肠道菌群能代谢 RSV。研究表明，人源肠道菌 Slackiaequolifaciens、Adlercreutziaequolifaciens[18]及动物源肠道菌 *Eggerthellalenta ATCC 43055*[85]将 RSV 转化为 DHR。另外，RSV 能直接影响肠道菌群组成，通过调节肠道菌群间接改善肥胖。RSV 能上调肥胖小鼠异杆菌属 (*Allobaculum*)，拟杆菌属(*Bacteroids*)，布劳特氏菌属(*Blautia*)及 *Parabacteroids* 菌属的丰度，下调脱硫弧菌属(*Desulfovibrio*)，*Lachnospiraceae_NK4A316_group* 菌属，另枝菌属(*Alistipes*)，变形杆菌属(*Proteobacteria*)，*Turicibacteraceae* 菌属及 *Moryella* 菌属的丰度[82-83,86]。

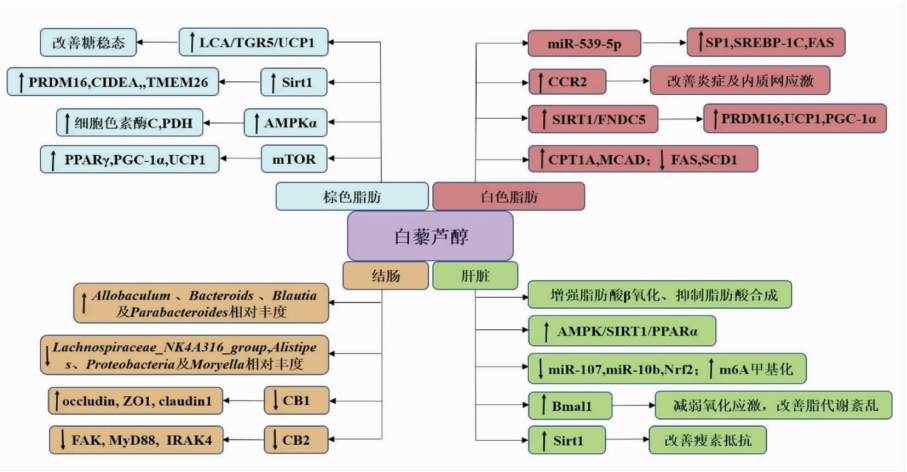


**图 3 白藜芦醇在脂肪组织、结肠及肝脏中调节肥胖**

Fig.3 Resveratrol mediated regulation of obesity in adipose tissue, colon and liver

研究者用抗生素干扰及粪菌移植的手段处理小鼠,发现 RSV 通过调节肠道菌群刺激机体产热[87],调节脂代谢[88]及发挥抗炎作用[89],进而改善肥胖。Liao 等[87]将补充 RSV 小鼠的粪便菌悬液灌胃给伪无菌小鼠,刺激了伪无菌小鼠的腹膜脂肪中 Sirt1 表达,增加了 PGC-1α,PPARγ,UCP1 的蛋白含量,使机体产热增加。

## 4 结语

本文从 RSV 的性质、代谢及改善肥胖的作用机理出发,对相关研究进行总结。RSV 改善肥胖的作用机理主要体现在调节脂代谢、刺激机体产热、抗炎及调节肠道菌群等方面。尽管对于 RSV 改善肥胖的研究虽已取得很大进展,但仍存在很多问题亟待解决。例如:1)RSV 的生物利用度低,在血液中检测到的 RSV 仅占摄入的 1%~8%,无法解释 RSV 对肥胖的保护作用。2)RSV 的干预时间、剂量及处理对象的性别可能对 RSV 的减肥作用有不同影响。基于以上问题,研究者应关注 RSV 的代谢产物在体内的分布及其生物活性,同时考虑试验对象性别、RSV 的干预时间及剂量是否会影响 RSV 的减肥效果,从而进一步解释 RSV 改善肥胖的作用机制,为 RSV 的实际应用场景提供更多试验和理论依据。

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## Research Progress in Resveratrol in Regulating Lipid Metabolism

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**Abstract** The imbalance between energy intake and energy consumption leads to the increase of adipose tissue and the disorder of lipid metabolism, which leads to obesity, diabetes, cardiovascular disease and other metabolic diseases. Resveratrol (RSV) is a natural astragalus polyphenols compound, which can effectively improve obesity and other metabolic diseases by regulating lipid synthesis and oxidative decomposition, adipokine secretion, adipose tissue heat production and inhibiting inflammation. At present, the regulation of lipid metabolism by RSV has attracted extensive attention and made great progress. Therefore, this paper reviews the recent studies on the regulation of lipid metabolism by RSV, in order to provide more theoretical basis for the application of RSV in improving metabolic diseases.

**Keywords** resveratrol; metabolite; fat metabolism; mechanism of action