·综 述·

知母黄柏药对治疗糖尿病骨质疏松症的药效物质和作用机制研究进展

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摘要：糖尿病骨质疏松症是由长期高血糖造成的全身代谢性骨病，已成为糖尿病的主要并发症之一，具有骨量减少、骨微结构破坏、骨脆性增加等特点。知母黄柏药对是一个经典中药配伍组合，在多数抗糖尿病骨质疏松症方剂中都有体现。现代药理研究表明，药对促进骨形成和抑制骨吸收的药效作用与 Nrf2、MAPK、Wnt、RANK/RANKL 信号通路及细胞自噬等密切相关。药对配伍能改变药效物质的溶出度和药动学，且药效物质有协同增效的作用。本文总结了知母黄柏药对的药效物质和抗糖尿病骨质疏松症作用机制，为该药对的进一步研究和开发提供参考。

关键词：知母；黄柏；药对配伍；糖尿病骨质疏松症；药效物质

中图分类号：R285　　**文献标志码：**A　　**文章编号：**1007-7693(2023)21-3039-08

DOI: 10.13748/j.cnki.issn1007-7693.20223030

引用本文：王芳，邓雪慧，许平翠，等. 知母黄柏药对治疗糖尿病骨质疏松症的药效物质和作用机制研究进展[J]. 中国现代应用药学, 2023, 40(21): 3039-3046.

Research Progress on Pharmacodynamic Substances and Mechanism of Anemarrhenae Rhizoma-Phellodendri Chinensis Cortex Herb Pair in the Treatment of Diabetic Osteoporosis

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ABSTRACT: Diabetic osteoporosis is a systemic metabolic bone disease caused by long-term hyperglycemia and has become one of the major complications of diabetes. It is characterized by decreased bone mass, destroyed bone microstructure, and increased bone fragility. Anemarrhenae Rhizoma-Phellodendri Chinensis Cortex herb pair is a classic drug combination, and has been widely used in many anti-diabetic osteoporosis prescriptions. The pharmacological studies have shown that the effects of this herb pair on promoting formation and inhibiting bone resorption are closely related to the Nrf2, MAPK, Wnt and RANK/RANKL signaling pathways as well as autophagy. The compatibility of this herb pair changes the dissolution and pharmacokinetics of the active substances, which have synergistic effects. This article summarized the effective substances of Anemarrhenae Rhizoma-Phellodendri Chinensis Cortex and its mechanism of action against diabetes and osteoporosis, providing a reference for further research and development of the drug pair.

KEYWORDS: Anemarrhenae Rhizoma; Phellodendri Chinensis Cortex; herb pair compatibility; diabetic osteoporosis; pharmacodynamic substance

糖尿病骨质疏松症(diabetic osteoporosis，DOP)是糖尿病并发的一种全身代谢性骨骼疾病，具有骨量减少，骨微结构破坏，骨脆性增加，易发生骨折等特点。糖尿病患者并发骨质疏松的风险比非糖尿病人群高 4~5 倍[1]，已成为长期严重疼痛和功能障碍的主要原因。DOP 的主要病因是长期高血糖引起糖基化终末产物(advanced glycation end products，AGEs)过度沉积，激活 AGEs 受体(receptor of advanced glycation end products，RAGE)，使成骨细胞(osteoblast，OB)主导的骨形成功能降低，破骨细胞(osteoclast，OC)主导的骨吸收功能过度，最终造成骨丢失[2]。DOP 的临床治疗注重降血糖、抗骨吸收和促进骨形成 3 个方面。

DOP 归于中医“消渴、骨痿”范畴，认为关键环节在于阴虚燥热，重视滋阴清热潜阳，以防燥热耗伤气阴，致津枯骨萎[3]。滋阴清热方药在 DOP 治疗方面已取得良好的临床疗效。知母黄柏药对(以下简称：“知柏药对”)出自金·李杲《兰室秘藏》。知母滋阴润燥，黄柏清热燥湿，皆属清热药，味苦性寒。二者相须为用，相互促进，滋阴清热功效得以增强，在经典方剂知柏地黄丸、龟鹿二仙汤、虎潜丸、大补阴丸等中作为核心组成。在中

基金项目：国家自然科学基金项目(81973447)；浙江省自然科学基金项目(LY21H280001)；浙江省中医药科技计划项目(2021ZQ018)

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医药治疗 DOP 中，以知柏药对为主的复方最为常用[4]。知母为百合科植物知母 *Anemarrhena asphodeloides* Bge.的干燥根茎，其主要成分为皂苷和黄酮类，另外有木质素、有机酸等[5]。黄柏为芸香科植物黄皮树 *Phellodendron chinense* Schneid.的干燥树皮，主要成分为生物碱类，此外有黄酮类、萜类、多糖类等[6]。本文综述了知柏药对的药效物质及其治疗 DOP 的研究进展。

1 知柏药对抗 DOP 的药效物质

1.1 知母皂苷

甾体皂苷及其苷元是知母的主要活性成分，以苷元结构分为螺甾皂苷类和呋甾皂苷类，知母皂苷 BII 的含量最高[5]。知母皂苷类成分有很好的降糖或抗骨质疏松活性作用[7-8]。体内研究证明，知母总皂苷能缓解去卵巢大鼠的骨丢失[9]。知母皂苷 BII 能够促进链脲佐菌素(streptozotocin，STZ)诱导大鼠模型的骨形成[10]。薯蓣皂苷元可以防止视黄酸诱导的大鼠骨质疏松症骨质流失[11]。体外研究证明，知母皂苷 BII 和知母皂苷元能促进 H_2O_2 诱导 OB 模型的细胞增殖活性[12]，增加 OB 分泌胶原蛋白 I，促进钙化结节形成[13]。知母皂苷 BII 还能抑制 OC 活性[14]。

1.2 知母黄酮

知母黄酮主要为双苯吡酮类，以芒果苷为代表。芒果苷口服后能降低糖尿病小鼠的血糖水平，改善葡萄糖耐量[15-17]，降低胰岛素抵抗，改善肾功能[18-19]，能用于治疗高胰岛素血症和 2 型糖尿病。芒果苷可以促进 OB 分化，并抑制 OC 活性[20]，具有显著的抗骨质疏松作用。新芒果苷对破骨细胞的形成分化有抑制作用，降低破骨细胞中组织蛋白酶的表达[21]。异芒果苷可以改善糖尿病小鼠的血脂代谢和糖耐量，减少炎症因子生成[22]。芒果苷元可以减弱肥胖小鼠的胰岛素抵抗[23]。

1.3 黄柏生物碱

生物碱是黄柏的主要药效成分[24]，代表性化合物为小檗碱。已有大量报道小檗碱及其衍生物在糖尿病、心血管疾病、炎症、精神疾病等方面的成功应用[25]。在骨质疏松症治疗方面，小檗碱口服给药后能显著改善由糖尿病[10]、衰老[26]、雌激素下降[27]和糖皮质激素诱导[28]等因素导致的骨密度下降、骨微结构破坏和骨生物力学性质变差等情况，提高骨形成指标碱性磷酸酶(alkaline phosphatase，ALP)、骨钙素(osteocalcin，OCN)等含量。木兰花碱可以降低去卵巢诱导[29]和炎症性小鼠骨质疏松模型[30]的骨吸收，提高骨密度。

1.4 活性多糖

知柏药对含有丰富的多糖成分。研究发现，知母聚糖能够显著降低四氧嘧啶诱导的高血糖[31]。笔者所在课题组前期从黄柏中分离出一种阿拉伯半乳聚糖，能改善糖尿病大鼠葡萄糖耐量，降低血糖与骨组织的 AGEs 含量，提高骨密度[32]。多糖具有含量高、安全性高等优点[33]，知柏药对的多糖类成分有潜力开发为保护 DOP 的药物或功能性食品。

2 知柏药对抗 DOP 的作用机制

2.1 降血糖作用

目前临床治疗 DOP 以控制血糖为前提[34]。葡萄糖苷酶抑制剂可以通过竞争性结合葡萄糖苷酶，抑制寡糖水解，降低餐后血糖，是目前糖尿病治疗药物的主要靶点之一[35]。笔者所在课题组发现黄柏多糖通过抑制葡萄糖苷酶活性，降低糖尿病大鼠血糖和骨组织 AGEs 沉积，进而提高骨密度[32]。

胰岛素敏感性受损会阻碍葡萄糖有效利用。知柏药对存在许多能够提高胰岛素敏感性和代谢稳态发挥降血糖作用的药效物质，典型化合物为小檗碱[36]。小檗碱可以激活丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)等信号通路增加胰岛 β 细胞功能、提高胰岛素敏感性[37]，降低 STZ 诱导大鼠的血糖和糖化血红蛋白，提高骨形成相关蛋白 Runt 相关转录因子 2(runt-related transcription factor 2，Runx2)、骨保护素(osteoprotegerin，OPG)和 OCN 的表达[10]。纳米载体修饰的芒果苷能保护 1 型糖尿病动物的胰岛 β 细胞，促进胰高血糖素样肽 1 分泌[38]。

知柏药对还可以通过改善肠道菌群紊乱来降低血糖。知柏药对能提高梭菌纲、拟杆菌属等有益菌丰度，降低乳酸杆菌、致病菌芽孢杆菌丰度，改善糖尿病造成的肠道菌群紊乱[39]，降低 HepG2 细胞的甘油三酯含量，提升糖耗量，促进糖脂代谢，最终降低 STZ 诱导糖尿病大鼠的血糖[40]。知柏药对还有其他降糖活性成分，如木兰花碱和知母皂苷元。木兰花碱可以促进胰岛 β 细胞分泌胰岛素来提高大鼠糖耐量[41]，下调脂肪细胞过氧化物酶体增殖剂激活受体-γ 和 CCAAT 增强子结合蛋白-α 减少脂肪形成[42]，抑制 α-葡萄糖苷酶[43]、糖醛还原酶[44]、蛋白酪氨酸磷酸酶 1B[45]活性降低血糖。另外，已有研究发现知母皂苷元可以通过抑制核因子 κB(nuclear factor kappa-B，NF-κB)信号通路改善肥胖小鼠脂肪细胞的胰岛素抵抗[46]。综上，知柏药对中

降糖活性成分很有可能成为抗 DOP 天然药物的重要来源。

2.2 促进骨形成作用

知柏药对中存在的多种活性成分(包括芒果苷、知母皂苷 BII、小檗碱等)，能够激活 OB 的骨形成功能，见表 1[20, 47-58]。

抗氧化途径是知柏药对修复骨形成功能的重要机制。临床研究证明，长期高血糖会导致 OB 氧化应激水平升高，抑制骨形成[59]。芒果苷能激活核因子 E2 相关因子 2(nuclear factor erythroid 2-related factor 2，Nrf2)信号通路，增强抗氧化酶活性，降低凋亡相关蛋白表达，提高氧化损伤 OB 模型的增殖活性[50]。小檗碱能降低 DOP 动物模型血清和骨组织丙二醛(malonaldehyde，MDA)水平，增加超氧化物歧化酶(superoxide dismutase，SOD)和谷胱甘肽过氧化物酶活性，减少过量活性氧，修复骨组织 DNA、脂质和蛋白质[60]。

长期高血糖引起的炎症在 DOP 的发生发展过程中发挥重要作用。经典炎症信号通路 NF-κB 和 MAPK 是 RAGE 下游的重要信号通路。知母皂苷 AIII 能够抑制 AGEs 诱导 OB 的 RAGE/MAPK 信号通路，降低白介素-1β(interleukin-1β，IL-1β)、白介素-6(interleukin-6，IL-6)和肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)水平，上调 ALP 和 OCN 水平，逆转四氧嘧啶引起斑马鱼的骨量丢失。分子对接预测得到知母皂苷 AIII 和 RAGE 之间存在相互作用[49]。小檗碱促进 p38 MAPK 的磷酸化和 Runx2 表达，提高 OB 增殖活性[61]。知母皂苷 BII 可以抑制糖尿病大鼠骨组织 mTOR 和 NF-κB 的磷酸化水平，激活 OB 自噬，减少细胞凋亡，发挥促进骨形成的作用[48]。

糖尿病环境会使骨髓间充质干细胞(bone marrow mesenchymal stem cells，BMSCs)倾向分化为脂肪细胞，分化为 OB 的能力下降，造成脂肪积累和骨质流失[62]。小檗碱能激活 Wnt/β-catenin 信号通路促进 BMSCs 的成骨分化并抑制其成脂分化，发挥抗 DOP 作用[63]。由此可见，修复 OB 和 BMSCs 功能是知柏药对促进骨形成作用的重要途径。

2.3 抑制骨吸收作用

高血糖环境会造成 AGEs 骨内蓄积，诱发炎症因子(IL-1α、IL-1β、IL-6 和 TNF-α)生成和大量蓄积，促进 OC 分化和骨溶解，破坏骨稳态[64-65]。知柏药对中的知母皂苷类、双苯吡酮类和生物碱类是抑制骨吸收的主要药效物质，见表 2。例如，知母皂苷元抑制 NF-κB 和 MAPK 通路减少 OC 分化，抑制骨吸收[66]。芒果苷抑制 NF-κB 和 Erk 信号通路，降低 RANKL 诱导的 OC 活性[20]。小檗碱抑制 NF-κB 和 Akt 通路，降低 RANKL 诱导 OC 分化[67]。四氢巴马汀拮抗 NF-κB 和 MAPK 信号通路，降低骨质疏松小鼠血清炎症因子(TNF-α 和 IL-6)和骨吸收标志物[I 型胶原 C 端肽和抗酒石酸酸性磷酸酶(tartrate-resistant acid phosphatase，TRAP)5b]水平，

表 1 知柏药对促进骨形成的活性成分

Tab. 1 Active components of Anemarrhenae Rhizoma-Phellodendri Chinensis Cortex herb pair that promoted bone formation

序号	化合物	来源	动物模型(给药剂量)	细胞模型(给药剂量)	作用	参考文献
1	知母皂苷元	知母	/	成骨细胞(osteoblast，OB)(0.01, 0.1, 1 μg·mL^{-1})	OB：ALP↑，矿化结节↑	[47]
2	知母皂苷 BII	知母	糖尿病大鼠(100, 300, 500 mg·kg^{-1}·d^{-1})	葡萄糖诱导 OB(0.1, 1, 10 μmol·L^{-1})	mTOR/NF-κB 磷酸化↓，自噬↑	[48]
3	知母皂苷 AIII	知母	四氧嘧啶诱导斑马鱼(0.01, 0.1, 1 μmol·L^{-1})	AGEs 诱导 OB(0.001, 0.01, 0.1, 1 μmol·L^{-1})	斑马鱼：骨骼矿化区域↑，甘油三酯↓，总胆固醇↓ OB：ALP↓，IL-1β↓，IL-6↓，OCN↑，RAGE/MAPK↓	[49]
4	芒果苷	知母	/	OB(1 000, 100, 10, 1, 0.1 μmol·L^{-1})	WST-1↑，ALP↑，Runx2↑，细胞增殖↑，骨吸收↓	[20]
5	芒果苷	知母	/	H_2O_2 诱导 OB(5, 10, 20 μmol·L^{-1})	凋亡↓，活性氧(reactive oxygen species，ROS)↓	[50]
6	芒果苷	知母	/	糖皮质激素诱导 OB(10, 20, 40, 60 μmol·L^{-1})	ROS↓，凋亡↓	[51]
7	薯蓣皂甙元	知母	STZ 诱导大鼠(50 mg·kg^{-1}·d^{-1})	/	血糖↓，ALP↑	[52]
8	小檗碱	黄柏	/	BMSCs (1, 5, 10 μg·mL^{-1})	BMSCs 分化为 OB↑	[53]
9	小檗碱	黄柏	/	H_2O_2 诱导 BMSCs(1, 3, 10, 30 μmol·L^{-1})	ROS↓，SOD↑，凋亡↓	[54]
10	小檗碱	黄柏	/	OB(5, 10, 20 μmol·L^{-1})	ALP↑，OCN↑，Runx2↑	[55]
11	小檗碱	黄柏	/	脂多糖诱导 BMSCs(1, 5, 10, 50, 100 μmol·L^{-1})	ALP↑，OCN↑，Runx2↑，脂质积聚↓，BMSCs 分化为 OB↑	[56]
12	巴马汀	黄柏	去卵巢小鼠模型 (1, 10 mg·kg^{-1})	OB(10 μmol·L^{-1})	小鼠：骨吸收↓；OB：RANKL↓	[57]
13	巴马汀	黄柏	/	BMSCs(117 μg·mL^{-1})	Runx2↑，ALP↑，OCN ↑	[58]

并抑制 RANKL 诱导 OC 分化[68]。木兰花碱抑制 MAPK 和 NF-κB 信号通路，减少炎症性骨吸收[30]。笔者所在课题组发现木兰花碱能进入 OB 和 OC 胞内发挥作用。

3 知柏药对的配伍作用影响

3.1 配伍对药效物质溶出程度的影响

药对配伍对药效物质的溶出度有显著影响[69]。邱昆成等[70]发现与知母单煎液相比，药对水煎液中芒果苷和知母皂苷 AIII 含量降低，新芒果苷含量升高。药物比例改变时，成分溶出度会发生变化，且等比例水煎液中新芒果苷含量最高。徐福平等[71]发现两药等量配伍时小檗碱的含量高于黄柏单煎液。以上工作为知柏药对在临床等量配伍提供了依据，但是对于药对配伍前后指纹图谱和其他成分含量变化方面的研究较少，有待进一步开展。

3.2 配伍对药效物质药动学的影响

共同存在的药效物质在配伍环境下会相互影响代谢过程。Lin 等[72]研究芒果苷的药动学发现，芒果苷单独给药时会在血浆和组织中迅速分布，胃和肠作为主要消化和吸收器官，含药浓度最高，即使在给药后 6 h，胃肠中仍存在蓄积。与单体给药组相比，知柏药对组血浆中芒果苷达峰时间从 1 h 延长为 4 h，生物利用度增长近 1 倍。与知母单煎液相比，知柏药对给药后芒果苷的体内消除速率无显著影响[73]。细胞药动学研究表明，知母组和药对组给药后芒果苷在大鼠胰岛素瘤细胞内的浓度高于单体给药组，且药对组的药时曲线下面积明显高于单体组和知母组，说明配伍后黄柏能够促进芒果苷进入细胞[74]。

3.3 配伍对药效作用的影响

知柏药对水煎液能显著改善糖尿病大鼠骨微结构，以等量配伍药效最佳[75]。代谢组学研究表明，知柏药对能够调控丙酸雌甾酮造模动物的花生四烯酸通路，且优于黄柏或知母单用组[76]。但是知柏药对对于 DOP 动物模型的代谢组学研究仍有待开展。

药效物质的配伍研究发现，小檗碱和知母皂苷 BII 联用的降糖效果优于二甲双胍[77]。芒果苷和小檗碱能以离子键形式形成复合盐，激活 HepG2 细胞 MAPK 信号通路，改善糖脂代谢[78]，促进 L6 成纤维细胞的葡萄糖摄取，优于单独使用一种成分的效果[79]，芒果苷、四氢表小檗碱、黄柏碱、木兰花碱、13-羟基小檗碱、巴马汀和小檗碱是知柏药对的入血成分，它们的组合物能够增加糖尿病斑马鱼的骨量，提高 ALP 活性，且成分间具有协同作用[75]。由上可知，配伍对知柏药对的抗 DOP 效果具有显著促进作用。

4 总结

知柏药对是抗 DOP 的经典用药，药效物质主要包括知母甾体皂苷类、知母双苯吡酮类、黄柏异喹啉生物碱类和多糖类。知柏药对的抗 DOP 药效物质主要作用机制包括降血糖、促进骨形成和抑制骨吸收 3 个方面，见图 1。

药对中的多数药效物质都具有控制糖尿病血糖水平的显著作用；在骨形成方面，甾体皂苷和双苯吡酮化合物通过抑制氧化应激或提高自噬水平激活 OB 活性，异喹啉生物碱通过促进 BMSCs 向 OB 转化等途径促进骨形成；在骨吸收方面，该药对的药效物质群大多通过抑制 OC 的 NF-κB 和 MAPK 等通路，降低炎症水平来降低骨吸收。

尽管知柏药对的抗 DOP 药效在临床和动物层面已经得到了证实，但是目前对于药效物质方面的研究和相关产品开发仍然相对薄弱。知母皂苷 BII、知母皂苷 AIII、芒果苷、小檗碱等活性物质，

表 2 知柏药对抑制骨吸收的活性成分

Tab. 2 Active components of Anemarrhenae Rhizoma-Phellodendri Chinensis Cortex herb pair that inhibited bone resorption

序号	化合物	来源	动物模型(给药剂量/μmol·L^{-1})	细胞模型(给药剂量/μmol·L^{-1})	作用	参考文献
1	知母皂苷元	知母	/	脂多糖诱导破骨细胞(osteoclast，OC)(1, 2, 4, 8)	NFATc1↓	[66]
2	知母皂苷 BII	知母	/	OC(2, 4, 8)	TRAP↓	[14]
3	巴马汀	黄柏	/	OC(1, 5, 10, 40, 100)	TRAP↓，NO_2↑	[56]
4	小檗碱	黄柏	/	OC(0.1, 1, 5)	TRAP↓，NFATc1↓	[67]
5	四氢巴马汀	黄柏	去卵巢小鼠(4.75，9.5，19)	/	NFATc1↓，TRAF6↓	[68]
6	小檗碱	黄柏	/	OC(0.1, 1, 10)	TRAP↓	[80]
7	小檗碱	黄柏	/	OC(15~45)	TRAP↓，IL-1β↓，IL-6↓，IL-23↓	[81]
8	小檗碱	黄柏	/	OC(0.25, 0.5, 1)	NFATc1↓，TRAP↓	[82]
9	巴马汀	黄柏	/	OC(10, 20, 40)	RANKL↓	[58]
10	木兰花碱	黄柏	钛颗粒诱导小鼠(2.5 mg·kg^{-1})	OC(200)	小鼠：TRAP↓，TNF-α↓，IL-1β↓ OC：NF-κB↓，NFATc1↓	[29]

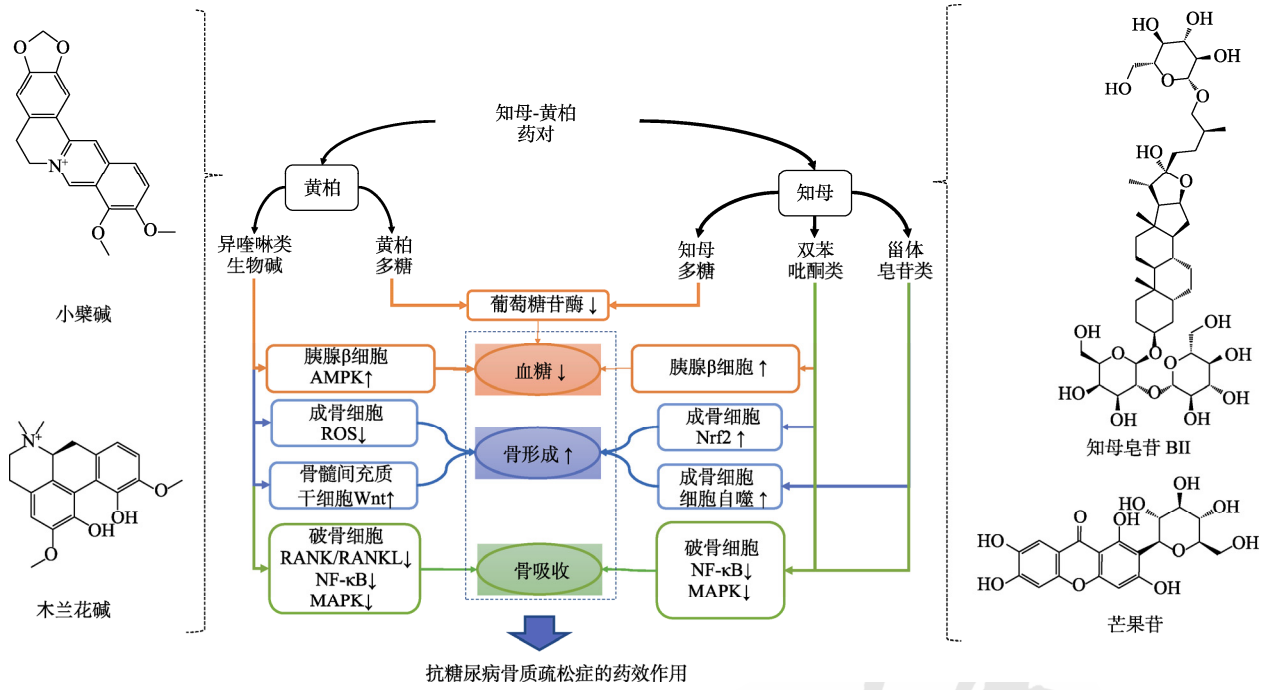

图 1 知柏药对的代表性活性成分及抗 DOP 作用机制

Fig. 1 Representative active compounds of Anemarrhenae Rhizoma-Phellodendri Chinensis Cortex herb pair and the related anti-DOP mechanisms

可以作为先导化合物进行开发，从而获得生物利用度更高、活性更优的产物，为抗 DOP 新药研究提供基础；对于知柏药对的配伍作用研究，可以采用网络药理学、代谢组学、系统生物学等多种技术考察药对协同增效的机制，探讨多成分、多靶点、多途径的治疗特点；此外，还需要开展知柏药对抗 DOP 循证医学研究，获得更多临床数据，为制定 DOP 临床治疗新策略提供可靠依据。

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收稿日期：2022-08-25
(本文责编：陈怡心)