

藏茵陈有效成分改善代谢综合征的作用机制研究进展[△]

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摘要 代谢综合征(MS)是以肥胖、糖脂代谢异常以及高血压为主要特征的临床症候群。藏茵陈是我国藏族民间常用药,其功效与MS病机吻合,对MS具有对症治疗潜力。本文对藏茵陈有效成分改善MS的作用机制进行总结发现,龙胆苦苷、獐牙菜苷、獐牙菜苦苷、芒果苷、齐墩果酸等有效成分可通过调节糖脂代谢、改善肥胖、调节心血管系统、抗慢性炎症、抗氧化应激、抗内质网应激、调节自噬、调节肠道菌群紊乱,发挥改善MS的作用。

关键词 藏茵陈;有效成分;代谢综合征;肥胖;糖脂代谢;作用机制

Research progress on the improvement mechanism of active ingredients of *Swertia mussotii* on metabolic syndrome

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ABSTRACT Metabolic syndrome (MS) is a complex group of clinical syndromes with obesity, abnormal glucose and lipid metabolism and hypertension as the main clinical features. *Swertia mussotii* is a commonly used medicine among the Tibetan people in China. Its efficacy is consistent with the pathogenesis of MS, which has the potential for symptomatic treatment of MS. It is found that effective ingredients such as gentiopicroside, sweroside, swertiamarin, mangiferin, and oleanolic acid can improve MS by regulating glucose and lipid metabolism, improving obesity, regulating the cardiovascular system, inhibiting chronic inflammation, oxidative stress, endoplasmic reticulum and autophagy, and improving intestinal microflora disorder.

KEYWORDS *Swertia mussotii*; active ingredients; metabolic syndrome; obesity; glucose and lipid metabolism; mechanism of action

代谢综合征(metabolic syndrome, MS)是一组以肥胖、糖脂代谢异常以及高血压等作为主要特征,严重影响机体健康的临床症候群,与肝肾损伤、骨关节炎、阿尔茨海默病等的发生密切相关^[1]。目前临床针对MS主要为单靶点的治疗模式,易导致患者服用药物种类多、经济负担大,且不良反应明显;而中医药在治疗MS方面具有多靶点、多层次、多途径调控的特点,具备独特优势。

藏茵陈作为“藏药八珍”之一,是藏药中治疗肝胆疾病的代表性药物,其真品药用基原植物川西獐牙菜 *Swertia mussotii* Franch 为龙胆科獐牙菜属二年生草本,主要分布在四川、西藏和云南等地。藏茵陈性凉、味苦,具有清热解毒、平肝利胆、补气利湿的功效^[2]。中医认为,MS病机以肝郁脾虚、湿热内蕴证最为常见^[3]。藏茵陈功效与MS病机吻合,预示藏茵陈用于MS具有对症治疗潜力。因此,笔者查阅相关文献,总结藏茵陈有效成分在改善MS方面的机制研究进展,以期MS的临床治疗提供参考。

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1 MS的病理机制

MS的病理机制非常复杂,包括胰岛素抵抗(insulin resistance, IR)、腹型肥胖(abdominal obesity, AO)、慢性炎症(chronic inflammation, CI)、氧化应激(oxidative stress, OS)、内质网应激(endoplasmic reticulum stress, ERS)、游离脂肪酸(free fatty acid, FFA)水平增高、肠道菌群(intestinal microflora, IM)紊乱、肾素-血管紧张素系统异常、自噬活性缺陷等^[4]。

2 藏茵陈的有效成分

藏茵陈的化学成分有獐牙菜苦苷、龙胆苦苷、獐牙菜苷等环烯醚萜类化合物,芒果苷、当药醇苷等咕吨酮类化合物,齐墩果酸等三萜类化合物,异荭草素等黄酮类化合物,其中环烯醚萜类化合物为主要有效成分^[5]。有研究将獐牙菜苦苷、龙胆苦苷、獐牙菜苷、芒果苷、齐墩果酸作为藏茵陈的质量标志物^[6],由此可知,这5种化合物可能是藏茵陈的药效物质基础。

3 藏茵陈有效成分改善MS的作用机制

3.1 调节糖脂代谢

糖脂代谢紊乱是MS的主要特征之一。MS的血脂异常通常表现为甘油三酯(triglyceride, TG)、总胆固醇、

FFA水平升高和高密度脂蛋白胆固醇水平降低;血糖异常则表现为IR、糖耐量减低和糖尿病^[7]。

温授惠等^[8]利用肝细胞脂肪变性体外模型研究发现,龙胆苦苷和獐牙菜苷可显著降低细胞内TG水平;其作用机制与激活AMP活化的蛋白质激酶(AMP-activated protein kinase, AMPK),上调脂质分解相关蛋白(脂酰辅酶A氧化酶1、肉毒碱棕榈酰基转移酶1A)表达,抑制脂质合成相关蛋白(胆固醇调节元件结合蛋白1、脂肪酸合成酶)和乙酰辅酶A羧化酶1表达有关。獐牙菜苦苷作为一种降糖降脂的重要先导化合物,能够减轻果糖诱导的非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)小鼠肝损伤和糖脂代谢紊乱,其调节糖脂代谢的机制与激活肝脏中核转录因子2相关因子2(nuclear factor-erythroid 2-related factor 2, Nrf2)信号通路,下调胆固醇调节元件结合蛋白1、脂肪酸合成酶和乙酰辅酶A羧化酶1表达有关^[9]。研究显示,芒果苷对链脲菌素(streptozotocin, STZ)诱导的糖尿病大鼠具有保护作用^[10]。芒果苷抗糖尿病分子机制较为复杂,包括促进糖酵解、降低血糖^[11];双重激活过氧化物酶体增殖物激活受体 γ (peroxisome proliferators-activated receptor γ , PPAR γ)/葡萄糖转运蛋白4(glucose transporter 4, GLUT4)信号通路,调节代谢水平^[12];促进胰岛再生并激活PPAR α 信号通路,改善IR^[13-14]。龙胆苦苷能够抑制STZ诱导的糖尿病小鼠肝脏糖脂代谢紊乱,还可明显改善小鼠糖脂代谢紊乱,其作用机制可能与抑制磷脂酰肌醇3激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, Akt)信号通路活性有关^[16]。齐墩果酸对糖尿病肾病大鼠具有改善作用,能降低大鼠血脂并减少肾脏脂肪堆积,其作用机制可能与调节AMPK/PPAR γ 共激活因子1 α (PPAR γ coactivator-1 α , PGC-1 α)信号通路和Toll样受体4(Toll-like receptor 4, TLR4)/核因子 κ B(nuclear factor- κ B, NF- κ B)信号通路相关^[17]。还有研究发现,齐墩果酸可减轻高脂饮食诱导的大鼠糖脂代谢紊乱^[18],显著降低NAFLD大鼠血清中TG、极低密度脂蛋白胆固醇含量^[19],还能通过调节肠-肝轴减轻NAFLD大鼠的代谢紊乱^[20]。

由此可知,藏茵陈有效成分龙胆苦苷、獐牙菜苷、獐牙菜苦苷、芒果苷、齐墩果酸可通过激活Nrf2、PPAR γ /GLUT4、AMPK/PGC-1 α 信号通路,抑制PI3K/Akt信号通路等,抑制脂质合成,促进脂质分解,从而调节糖脂代谢,改善MS。

3.2 改善肥胖

肥胖是MS的关键危险因素和重要环节。肥胖状态下的脂肪组织表现出脂肪细胞数量增多、体积肥大,随着疾病进展还会出现巨噬细胞浸润增加和脂肪细胞因子分泌异常,从而加速IR和炎症的形成^[21]。

獐牙菜苦苷能够诱导肥胖小鼠脂肪组织褐变产热,从而减少骨骼肌脂肪堆积^[22]。獐牙菜苷可改善小鼠肥胖,其作用机制与调节PPAR α 表达相关^[23]。龙胆苦苷可以抑制高脂饮食诱导的小鼠体重增长和内脏脂肪增加,其作用机制可能与抑制脂肪生成相关基因表达有关^[24]。芒果苷不仅可减少小鼠前脂肪细胞(3T3-L1)中TG的积聚,还可同时调节脂肪生成相关基因表达,包括抑制乙酰辅酶A羧化酶基因表达、上调叉头框蛋白O1基因表达^[25]。

由此可知,藏茵陈有效成分獐牙菜苦苷、獐牙菜苷、龙胆苦苷可通过调节PPAR α 、脂肪生成基因的表达,减少脂肪堆积,进而改善MS。

3.3 调节心血管系统

血压升高是MS最常见的病理变化,可导致心血管疾病(cardiovascular disease, CVD)的发生风险显著增加。獐牙菜苦苷对心血管系统病变具有保护作用,其效应包括抗动脉粥样硬化、抗炎等,其作用机制可能与调节心肌重构相关信号通路活性有关^[26]。相关研究发现,芒果苷能够降低高尿酸诱导的实验性高血压,其作用机制可能与改善血管内皮功能、促进一氧化氮释放有关^[27]。齐墩果酸可显著抑制血管紧张素转化酶(angiotensin converting enzyme, ACE)活性,具有开发成为新型降压药的潜力^[28]。齐墩果酸还可下调糖尿病大鼠C反应蛋白表达水平,降低平均动脉压,从而降低大鼠CVD发生风险^[29]。

由此可知,藏茵陈有效成分獐牙菜苦苷、芒果苷、齐墩果酸可通过调节心肌重构,改善血管内皮功能,从而调节心血管系统,改善MS。

3.4 抗CI

MS伴随的肥胖不仅可诱导CI,还可引发免疫细胞聚集,从而释放过量的炎症因子(如肿瘤坏死因子 α 、白细胞介素6等),进而诱导动脉粥样硬化、血脂异常、IR和高血压等MS的系列并发症的发生^[30]。獐牙菜苦苷能够抑制促分裂原活化的蛋白激酶(mitogen-activated protein kinase, MAPK)/NF- κ B信号通路的活化,从而减轻高脂饮食诱导肥胖小鼠的CI^[31]。芒果苷能够下调NAFLD小鼠炎性小体表达,抑制AMPK信号通路激活,进而减轻肝细胞焦亡和炎症反应^[32]。齐墩果酸可以减轻高脂饮食诱导的小鼠脂肪组织慢性炎症反应,其作用机制可能与抑制MAPK信号通路激活有关^[33]。异荛草素则可通过抑制糖原合成酶激酶3 β (glycogen synthase kinase 3 β , GSK-3 β)信号通路活性改善阿尔茨海默病小鼠的中枢神经炎症损伤^[34]。

由此可知,藏茵陈有效成分獐牙菜苦苷、芒果苷、齐墩果酸、异荛草素可通过抑制MAPK/NF- κ B、AMPK、GSK-3 β 信号通路活性,下调炎性小体表达,从而减轻CI,改善MS。

3.5 抗OS

OS被认为是MS的发生机制之一,也是MS的早期诱因。在心肌梗死大鼠中,獐牙菜苦苷可以降低大鼠心肌组织中OS标志物的水平并增强心肌抗过氧化能力^[35]。獐牙菜苦苷可以激活大鼠肝脏Nrf2/血红素加氧酶1(heme oxygenase-1,HO-1)信号通路从而上调抗氧化基因表达^[36]。王保等^[37]研究发现,獐牙菜苦苷可通过抑制还原型辅酶Ⅱ氧化酶(NADPH oxidase,NOXs)/活性氧(reactive oxygen species,ROS)轴,减少ROS生成,从而减轻STZ诱导的糖尿病大鼠周围神经痛。异荜草素对急性肾损伤小鼠具有保护作用,其作用机制可能与激活Nrf2信号通路、抗OS损伤有关^[38]。乳鼠在新生阶段短期摄入齐墩果酸,也可减少高糖诱导的骨骼肌OS损伤^[39]。

由此可知,藏茵陈有效成分獐牙菜苦苷、异荜草素、齐墩果酸可通过激活Nrf2/HO-1信号通路,抑制NOXs/ROS轴,从而减轻OS,改善MS。

3.6 抗ERS

内质网是一个参与脂质和蛋白质代谢的大型膜性网络,缺氧、错误折叠和/或突变的蛋白积聚、高糖均可诱发ERS,从而触发IR、CI、凋亡、胰岛素分泌减少、糖异生、脂肪生成增加等多种病理过程。芒果苷能够明显改善急性肝损伤小鼠的ERS,其作用机制可能与调节miR-20a/miR-101a-Nrf2信号通路有关^[40]。芒果苷还能减轻甲醛诱导的小鼠海马细胞ERS,抑制ERS相关标志物如葡萄糖调节蛋白78和ERS相关蛋白的表达水平^[41]。齐墩果酸则可通过激活肿瘤坏死因子受体相关蛋白1表达,减轻赭曲霉毒素A诱导的肾小管上皮HK2细胞ERS,从而抑制肾小管细胞凋亡^[42]。

由此可知,藏茵陈有效成分芒果苷、齐墩果酸可通过调节Nrf2信号通路,抑制ERS相关蛋白表达以及激活肿瘤坏死因子受体相关蛋白1,从而减轻ERS,改善MS。

3.7 调节自噬

自噬是维持细胞器功能和细胞内营养环境的关键,参与维系全身代谢稳态,自噬失调可导致或加速代谢紊乱的发生发展。獐牙菜苦苷可以减轻乌头碱诱导的H9c2心肌细胞损伤,稳定线粒体膜电位并抑制自噬基因的表达^[43]。獐牙菜苦苷还能增强NAFLD小鼠肝脏的自噬水平,其作用机制与激活AMPK/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)信号通路有关^[44]。芒果苷能增强高糖诱导的心肌细胞的自噬水平,减轻心肌细胞的损伤程度,其作用机制可能与降低mTOR磷酸化水平有关^[45]。芒果苷还能促进高脂饮食诱导的肥胖症小鼠肝脏中自噬因子(如自噬相关蛋白7和成纤维细胞生长因子21)的表达^[46]。在体外研究中,齐墩果酸可通过增强自噬来减轻高糖诱导的大鼠肾小管上皮NRK-52E细胞纤维化^[47]。

由此可知,藏茵陈有效成分獐牙菜苦苷、芒果苷、齐墩

果酸可通过调节自噬相关因子表达,激活AMPK/mTOR信号通路,从而调节自噬水平,改善MS。

3.8 调节IM紊乱

IM紊乱是MS发生发展的潜在病因之一,一旦IM与宿主免疫系统间的平衡被破坏,则可导致全身性炎症反应以及IR。He等^[48]研究发现,芒果苷可通过促进有益菌(阿克曼氏菌、副拟杆菌、双歧杆菌)生长,抑制有害菌(幽门螺杆菌)生长,增加机体短链脂肪酸的生成,从而减少动脉斑块。齐墩果酸具有改善IM的作用,Xue等^[49]运用测序技术发现齐墩果酸能够增加小鼠肠道潜在有益菌(颤螺菌、热纤梭菌)的相对丰度,从而维系肠道正常生理功能。Yuan等^[50]证实异荜草素能够抑制肠道炎症相关菌(另枝菌、幽门螺杆菌)生长。

由此可知,藏茵陈有效成分芒果苷、齐墩果酸和异荜草素可通过促进有益菌生长,抑制有害菌生长,从而调节IM紊乱,改善MS。

4 结语

藏茵陈有效成分可以通过调节糖脂代谢、改善肥胖、调节心血管系统、抗炎、抗OS、抗ERS、调节自噬和IM等改善MS。然而,现有研究多探讨藏茵陈中獐牙菜苦苷、芒果苷、齐墩果酸等有效成分对MS的改善作用,而其他有效成分是否参与改善MS以及改善MS的作用机制等仍不清楚,后续仍需要进一步探明藏茵陈改善MS的分子靶点、信号通路以及药效物质基础。鉴于MS在全世界的患病率逐年上升,未来将藏茵陈用于治疗MS这一常见的慢性病无疑是兼具社会效益和经济价值的。

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