

水飞蓟素防治代谢综合征的作用机制研究进展

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摘要

目的: 水飞蓟种子中含有大量的黄酮类化合物, 主要为水飞蓟素。本文对水飞蓟素防治代谢综合征的作用机制以及研究进展进行综述。为研发以防治代谢综合征为主要作用的药品或保健药食提供科学依据。方法: 查阅有关水飞蓟素防治代谢综合征的相关文献, 并系统总结与梳理。结果: 水飞蓟素具有调节血脂、降低血糖、抗炎、抗肿瘤、抗氧化、抗凝血、抗动脉粥样硬化等药理作用, 可以改善氧化应激、改善胰岛素抵抗(IR)、肥胖、保护血管内皮、改善肠道菌群、抑制血小板聚集、抑制炎症因子表达。结论: 水飞蓟素作为无肝脏不良反应的保肝降脂药, 具有抗氧化、抗炎、防治代谢综合征等功能, 有望成为新型有效的保健食品。

关键词

水飞蓟素, 代谢综合征, 药理靶点, 作用机制

Research Progress on the Mechanism of Silymarin in Preventing and Treating Metabolic Syndrome

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Abstract

Objective: The seeds of silymarin contain a large amount of flavonoids, mainly silymarin. This

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article reviews the mechanism of action and research progress of silymarin in the prevention and treatment of metabolic syndrome to provide a scientific basis for the development of drugs or health supplements with the main function of preventing and treating metabolic syndrome. Method: We review relevant literature on the prevention and treatment of metabolic syndrome with silymarin, and systematically summarize and sort it out. Results: Silymarin has the pharmacological effects of regulating blood lipids, lowering blood sugar, anti-inflammatory, anti-tumor, antioxidant, anticoagulant, anti atherosclerosis, etc. It can improve oxidative stress, improve insulin resistance (IR), obesity, regulate lipid metabolism, protect vascular endothelium, improve intestinal flora, inhibit platelet aggregation, and inhibit the expression of inflammatory factors. Conclusion: Silymarin, as a liver protective and lipid-lowering drug without adverse liver reactions, has functions such as antioxidant, anti-inflammatory, and prevention and treatment of metabolic syndrome, and is expected to become a new and effective health food.

Keywords

Silymarin, Metabolic Syndrome, Pharmacological Target, Mechanism of Action

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1. 引言

代谢综合征(metabolic syndrome, MS)又称胰岛素抵抗综合症,是人体内蛋白质、脂肪、碳水化合物等物质代谢紊乱的统称。1988 年美国斯坦福大学教授首次提出“x 综合征”的概念,后来称之为代谢综合征[1]。依据三大权威机构即美国心脏协会(American Heart Association, AHA)、国际糖尿病联合会(International Federation of Diabetes, IDF)和国家心肺血液研究所(National Institute of Cardiopulmonary and Hematology, NHLBI)共同认定,同时发生以下至少三种情况:向心性肥胖、血脂异常、糖代谢受损、血压升高和水平的高密度脂蛋白胆固醇(High-Density Lipoprotein Cholesterol),即可认定为 MS [2]。据研究显示,中国 18 岁以上的成人中,代谢综合征患病率为 33.9%,其影响相关疾病的发生也显著升高,可造成多种疾病增加,如高血压、冠心病、脑卒中、甚至某些癌症,包括性激素有关的乳腺癌、子宫内膜癌、胰腺癌等[3][4]。其中胰岛素抵抗和氧化应激是其发展的关键环节。从中医角度,MS 是由于脾虚湿盛,情志不疏致水谷津液气化输布失常,气机失调[5]。多种消积导滞、燥湿化痰、泄浊降脂以及疏肝健脾药等对 MS 具有防治作用。水飞蓟素具有健脾消食、行气散瘀、清热解毒、疏肝利胆、化浊调脂的作用,是有效的健胃消食药、护肝利胆药[6]。

水飞蓟素具有调节血脂、降低血糖、抗炎、抗肿瘤、抗氧化、抗凝血、抗动脉粥样硬化等药理作用[7]。所以该药有望成为一个无肝脏不良反应的降脂药。水飞蓟最早可追溯到公元 40~90 年,古罗马时期的著名医生和药理学家佩达努思·迪奥斯科里德斯最先将其定义为 Silybum,可食用,同时能治疗肝脏疾病[7]。大量实验和临床研究证明水飞蓟素能抗氧化、改善胰岛素抵抗,抗动脉粥样硬化,对心血管疾病有良好的治疗作用[8]。由于我国水飞蓟的栽培优良,分布广泛,黑龙江 70%的高产量,对于水飞蓟的成分以及临床研究不断增加,证实水飞蓟素具有一定的防治 MS 作用[9]。本文针对水飞蓟以及水飞蓟素等相关成分对代谢综合征的作用及机制进行综述,以期研发水飞蓟相关保健品及其在防治 MS 的应用方面提供参考[10]。

2. 水飞蓟的主要化学成分

水飞蓟化学成分研究始于 20 世纪 60~80 年代末, 德国科学家从水飞蓟中提取的有效成分水飞蓟素, 是一种含有水飞蓟宾、次水飞蓟素、异水飞蓟宾、水飞蓟宁的黄酮木脂素的复杂混合物[11]。水飞蓟气微味淡, 是具有良好的抗氧化、抗炎活性的护肝药物。其中水飞蓟宾(silybin)占总提取物的 50%~70%, 可降低氧化应激及其造成的细胞毒性[12]。

3. 水飞蓟素在防治 MS 中体现的保健功能

水飞蓟、水飞蓟素、水飞蓟宾以及黄酮类化合物与各种中药配伍的实验证实, 水飞蓟素能够发挥调血脂、降血糖、抗动脉粥样硬化、抗肿瘤作用[13]。对 MS 具有明显防治作用。

3.1. 调血脂

水飞蓟素能够显著降低血清或动物肝脏中 TG、TC 水平[14]。有实验结果显示, 水飞蓟素可显著降低高脂模型小鼠 TG 水平[15]。同时, 也显著降低了低密度胆固醇[LDL-C]和低密度脂蛋白胆固醇[VLDL-C]水平。水飞蓟素能明显降低高脂血症患者的甘油三酯含量。与此同时, 水飞蓟素也可显著升高高密度脂蛋白胆固醇[HDL-C]水平[16]。而随着 HDL-C 水平的升高, 也会加速血脂的代谢[17]。

3.2. 改善血糖水平

有研究显示, 水飞蓟素有助于 2 型糖尿病患者控制血糖, 可使糖化血红蛋白[HbA1c]显著降低, 同时显著升高血清胰岛素水平[18]。此外, 黄庆玲[19]等研究表明, 水飞蓟素能降低链脲佐菌素诱导糖尿病大鼠模型的血清过氧化脂质[LPO]和晚期糖基化终末产物[AGE]水平, 抑制肾脏组织非酶糖化及氧化产物生成, 防治糖尿病肾病。但另有研究发现[20], 水飞蓟素对四氧嘧啶致小鼠高血糖有显著降血糖作用, 而对链脲佐菌素诱导高血糖小鼠均没有降血糖作用。水飞蓟素还有助于提高胰岛素敏感[21]。

3.3. 抗动脉粥样硬化

动脉壁内皮损伤和脂质沉积是目前认为的动脉粥样硬化始动因素[22]。高血压、高脂血症等等刺激发生损伤后, 发生功能改变和渗透性增高。张亚茹等[23]研究表明, 水飞蓟油能够降低血浆胆固醇, 防治实验性主动脉粥样硬化有显著作用。

3.4. 抗肿瘤作用

癌症是长期共同作用引发的基因异常疾病, 由环境中的致癌物质和自身因素共同作用引发基因异常改变, 形成恶性肿瘤[24], 是一种慢性积累到急性质变的过程, 机体受到多种因素的共同作用, 发生基因异常改变, 形成癌症。研究证实[25], 水飞蓟素可抑制脑胶质瘤的生长从而作为一种潜在的抗恶性胶质瘤制剂。另外还有研究表明[26]可用于提高各种癌症类型的抗癌效果, 特别是在胃肠道吸收较差的情况也能通过激活 KEAP1/NRF2/ARE 和抑制 NF- κ B 信号通路发挥抗氧化作用而非清除自由基。水飞蓟素与拓扑异构酶 II 抑制剂米托蒽醌的生长抑制效应可产生协同作用, 能降低人前列腺癌细胞 PC-3 的存活率, 促进癌细胞凋亡[27]。

4. 水飞蓟素在防治 MS 中的药理靶点及作用机制

4.1. 改善氧化应激

研究表明, 机体内多氧自由基过多会引发一系列脂质过氧化的链式反应。氧化应激是指人体内原本

处于动态平衡的氧化还原态,因体内外因素如年龄、致病、药物或不健康的生活方式等,引起产生过多氧化态物质-活性氧簇[ROS]将还原态物质消耗殆尽[28],原本的动态平衡趋向氧化态引起的应激损伤。常见的 ROS 有单线态氧,过氧化氢氧、羟基自由基、超氧化物、一氧化氮、过亚硝酸根等,水飞蓟素通过促进血管平滑肌和炎症细胞的生长和迁移、降解细胞外基质、促进内皮细胞凋亡、激活转录因子(NF- κ B、AP-1)、促进炎症因子和黏附分子(ICAM-1, VCAM-1, E-选择素)过表达等方式损伤内皮细胞。ROS 增加胞质内钙离子浓度,减少调节血压稳定性作用的一氧化氮的生成,使血管舒张作用减弱。在氧化应激受损的 HepG2 细胞和 PC12 细胞中,水飞蓟素处理后可使造模细胞的异常下降的 MMP 和失活的复合体得到恢复,并有助于调节线粒体膜的通透性。水飞蓟素也能够抑制 NOX2/4、XOs 或通过抑制 iNOS 的解偶联来防治 ROS 过度产生。水飞蓟素通过提高机体抗氧化功能、增加抗氧化物酶的表达、改善脂质过氧化、清除自由基的方式来改善氧化应激[29]。

4.2. 改善胰岛素抵抗(IR)

胰岛素抵抗是糖尿病的发病机制,是发展为 2 型糖尿病的重要危险因素。水飞蓟素抗糖尿病的药理靶点和机制有三种[30]:上调雌激素受体阿尔法表达;激活十二指肠-脑-肝轴通路;稳定蛋白质结构。水飞蓟素通过抑制糖尿病大鼠主动脉组织非酶糖化及氧化从而改善胰岛素抵抗和控制糖尿病慢性血管并发症[31]。

4.3. 肥胖

肥胖是胰岛素抵抗和高胰岛素血症引起代谢后果的完美体现。胰岛素可强力促进脂肪细胞生长。以胰岛素抵抗和炎症为首的代谢综合征胰岛素抵抗伴随而来的是一种代偿性高胰岛素血症。高胰岛素水平会使胰岛素受体饱和,糖无法进入细胞,过多的糖分会被转化为甘油三酯进入循环系统[32],同时高胰岛素血症会使肝脏合成甘油三酯 TG 增加,抑制 HDL-C 合成。水飞蓟素可使患者减重[33]。

4.4. 保护血管内皮

当血管内皮细胞(VEC)与溶血磷脂酰胆碱(LPC)或黄嘌呤和黄嘌呤氧化酶(X + XO)共孵育 24 h 时,表现为细胞乳酸脱氢酶(LDH)泄漏量增多[34],细胞内 MDA 含量升高,NO 含量减少细胞生长减缓,存活率下降,当加入不同浓度水飞蓟素及黄酮类化合物后可明显抑制细胞 LDH 的泄漏量,降低 MDA 含量,提高 NO 的含量,从而对细胞起保护作用[5]。水飞蓟素还可有效保护人体内皮细胞免受低密度脂蛋白(OX-LDL)的损伤。水飞蓟素高、中、低剂量均能显著降低模型大鼠血液 ALT、AST、UA、TCHO、TC、LDL-C, ET-1 含量,具有良好的调节机体血脂水平作用,有效预防高脂血症和保护血管内皮细胞[35]。李凌等[36]研究发现水飞蓟素可通过下调 VEGF 抑制高糖刺激诱导血管内皮细胞增殖和迁移。

4.5. 改善肠道菌群

《黄帝内经》:“小肠者,受盛之官,化物出焉。”在《重订广温热论》记载:“消化法,消者,去其壅也;化者,导其滞也。”肠道菌群在促进营养物质的消化和吸收方面发挥重大作用[37]。肠道微生物群在辅助消化和吸收营养方面起着至关重要的作用。段素芳等研究显示,高剂量的水飞蓟素和麦芽组对动物肠道菌群有一定的改善作用,能促进产 SCFA 特定菌属的生长,提高肠道 SCFA 含量,改善肠道组织形态,从而改善维生素缺乏肠道吸收功能[38]。

4.6. 抑制血小板聚集

血小板聚集是动脉粥样硬化性疾病发展和其并发症产生的主要原因。水飞蓟素与泽泻抗血小板聚集

有协同作用。Guo [39]等发现水飞蓟宾等黄酮类物质能减轻血栓湿重, 抑制其聚集发挥抗血栓作用。

4.7. 抑制炎症因子表达

Xu [40]等研究表明水飞蓟素等黄酮类物质具有保护大鼠肾缺血再灌注损伤作用, 该作用与活化 Nrf2/HO-1 信号通路, 阻止 NF- κ B p65 核转位, 进而降低氧化应激水平和抑制炎症反应有关。水飞蓟素能够抑制炎症反应[41], 其机制可能是通过上调 miR-199a-3p 表达、抑制 p38MAPK/NF- κ B 通路实现的。

5. 总结与展望

水飞蓟味苦, 性凉, 归肝胆经。具有清热解毒, 疏肝利胆的功效, 中药具有多成分、多靶点、整体施治的特点, 就水飞蓟素防治代谢综合征而言, 其相关作用机制与临床表现之间的对应关系复杂多样。水飞蓟素可通过调节[42]与脂质代谢相关的酶、受体活性及其表达反应等调节血脂水平、同时水飞蓟素也可作用于胰岛素、肠道菌群、抗氧化酶、自由基等, 改善胰岛素抵抗、改善肠道菌群、改善氧化应激, 减少氧化型 LDL 的产生, 对高脂血症的防治具有显著作用。同时水飞蓟素可改善胰岛素抵抗, 增加胰岛素浓度, 降低高血糖水平[43]。水飞蓟素通过降血脂、降血糖以及促进消化等可显著改善患者肥胖程度。此外, 水飞蓟素对动脉粥样硬化具有显著改善作用, 降低心肌梗死及卒中等风险[44]。具有很大的临床研究价值与潜力。

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