综述

熊果酸的生物活性研究进展

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摘 要：熊果酸是一种天然存在的三萜类化合物，具有广泛的生物活性，可调血脂、抗炎、抗癌、抗氧化、保护心脏、肝脏、抗骨骼肌萎缩、抗病毒等。熊果酸众多的生物功能使其成为新的预防及治疗多种疾病有前途的候选物。另外，我国有丰富的植物中医药资源，熊果酸可以从许多常见植物中获得，比如沙棘、薰衣草、苹果的果皮等。熊果酸及其合成衍生物也涉及一系列与疾病预防相关的领域。因此，探讨熊果酸的功能性作用对应用于临床具有十分重要的意义。本文总结熊果酸的功能性作用及相关机制从而为治疗及预防其他疾病提供新的思路。

关键词：熊果酸；生物活性；机制；疾病
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Research progress on biological activity of ursolic acid

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Abstract: Ursolic acid is a naturally occurring triterpenoid compound with a wide range of biological activities, such as blood lipids regulation, anti-inflammatory, anti-cancer, anti-oxidation, heart and liver protection, anti-skeletal muscle atrophy, anti-virus, *etc*. Due to its numerous biological functions, it has become a promising candidate for the prevention and treatment of various diseases. In addition, China has abundant plant resources of traditional Chinese medicine. Ursolic acid can be obtained from many common plants, such as sea buckthorn, lavender and apple peel. Ursolic acid and its synthetic derivatives are also involved in a series of fields related to disease prevention. Therefore, it is very important to explore the functional role of ursolic acid for clinical use. This article summarizes the functional effects of ursolic acid and related mechanisms to provide new ideas for the treatment and prevention of other diseases.

Key words: Ursolic acid; biological activity; Mechanism; disease

熊果酸（Ursolic acid，UA），又名乌苏酸，化学名：3β-羟基-乌苏烷型-12-烯-28-羧酸，多以游离或与糖结合成苷的形式存在于沙棘、女贞子、山楂、蔓越莓、枇杷叶等植物中，化学式为 $C_{30}H_{48}O_3$，分子量为456. 71 g/mol，酸性，针状或结晶固体，熔点 283～285 ℃，最大紫外吸收波长约 450 nm[1]，UA 难溶于水，可溶于热冰醋酸和酒精氢氧化钠[2]，具有广泛的生物活性，可以破坏肿瘤细胞，调节脂质代谢，防止血管生成和转移，促进细胞分化，并且使健康组织免受肿瘤形成的炎症和氧化应激的影响，具有多种细胞内和细胞外靶点[3]。

1 调节血脂作用

脂代谢紊乱是许多慢性疾病包括动脉粥样硬化、心血管疾病、2 型糖尿病、非自然衰老和非酒精性脂肪肝（Nonalcoholic Fatty Liver Disease，NAFLD）发生的共同病理基础。大量研究表明，UA 是一种理想的、天然的、对正常细胞低毒性且能够有效改善糖脂代谢紊乱，提高胰岛素敏感性，调节代谢相关酶类的表达，进而改善肥胖、动脉粥样硬化、糖尿病以及延缓 NAFLD 进展等的新型植物化合物[4]。用

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50～200 mg/kg的UA灌胃高脂C57BL/6J小鼠，发现UA通过抑制磷酸二酯酶活性增强脂肪细胞的脂解作用，减少了机体脂质积累，还可以通过激活AMPK信号通路降低脂质含量，抑制乙酰辅酶a羧化酶（Acetyl CoA carboxylase，ACC）、脂肪酸合酶（Fatty acid synthase，FAS）、3-羟基-3-甲基戊二酰-CoA还原酶（HMGCR）等脂肪合成相关基因的表达，增强了白细胞分化抗原36（Cluster of differentiation 36，CD36）、过氧化物酶体增殖激活受体α（Peroxisome proliferators-activated receptorsα，PPARα）、肉碱棕榈酰转移酶1（Carnitine palmitoyltransferase 1，CPT1）和酰基辅酶a氧化酶1（Acyl coenzyme a oxidase，ACOX1））等脂肪分解相关基因及体内腺苷酸活化蛋白激酶（Amp-activated protein kinase，AMPK）蛋白的表达[5-6]。Lin等用10 μmol/L的UA干预肝细胞发现，UA可以通过抑制LXRαSREBP-1c信号通路相关基因（SREBP-1c、FAS、SCD、ACC、ACLY和FAE）的表达来调控肝细胞的脂质代谢降低细胞TG浓度[7]；10和50 mg/kg UA灌胃SD大鼠均能改善其衰老状况及肝脏脂质沉积，降低自然衰老大鼠肝质量和TG含量以及血浆TG和胰岛素含量[8]。在高脂饲料中添加0.5% UA可以降低大鼠骨骼肌游离脂肪酸和TG含量，通过解偶联蛋白3（Uncoupling protein 3，UCP3）/AMPK依赖途径的氧化，促进游离脂肪酸的吸收和β-氧化并减少骨骼肌细胞内的脂肪储存，并增强了游离脂肪酸代谢关键蛋白的表达（磷酸化AMPK（p-AMPK）、CD36、磷酸化-ACC（p-ACC）、肉毒碱棕榈酰转移酶-1（CPT-1）和UCP3的表达[9]。

2 抗炎作用

炎症反应本质是机体对外界刺激的一种防御，但是有些情况下，炎症反应成为一些疾病的发病基础，过于剧烈时甚至可以威胁生命，而熊果酸在多种疾病的研究中都表现出较好的抗炎活性。

2.1 代谢性疾病中的抗炎作用

代谢性疾病主要由代谢紊乱引起的。口服150 mg/d UA可以使代谢综合征患者症状缓解，体质量、BMI、腰围和空腹血糖降低，并提高了胰岛素敏感性[10]。糖尿病肾病小鼠灌胃UA 25 mg/kg后发现UA通过TLR4介导的炎症途径降低肿瘤坏死因子α（Tumor necrosis factor，TNF-α）、白介素-1β（Interluekin-1β，IL-1β）、IL-6和IL-18的水平，减轻炎症并预防了糖尿病肾病的发生；用10^{-5} mol/L UA干预巨噬细胞后可降低脂多糖（Lipopolysaccharide，LPS）刺激的巨噬细胞中炎症因子TNF-α、IL-6和IL-1β的分泌并阻断TLR4/MyD88通路[11]，急性肾损伤小鼠灌胃UA 100 mg/kg后发现通过增加了LC3B和Beclin-1的表达而增强巨噬细胞的自噬，通过诱导自噬治疗急性肾损伤发挥抗炎活性[12]；灌胃20 mg/kg UA可有效改善溃疡性结肠炎小鼠结肠损伤，降低血清中IL-1β和TNF-α水平以及结肠组织中NF-κB p65的高核水平[13]；在饲料中添加0.05%和0.2% UA均可抑制HFD喂养的$LDLR^{-/-}$小鼠动脉粥样硬化病变的发展，减缓体质量增加并减少小鼠体内巨噬细胞的募集[14]。

2.2 神经性疾病中的抗炎作用

熊果酸通过抗炎作用保护神经，治疗神经退行性疾病、缺血性脑血管病和脊髓损伤等[15]。灌胃100 mg/kg UA可以调节大鼠脑缺血中的炎症反应，通过激活核因子-红细胞2相关因子2信号通路改善脑水肿和脑外伤后神经功能不全[16]；灌胃25 mg/kg UA后显著降低了1-甲基-4-苯基-1，2，3，6-四氢吡啶诱导的小鼠神经炎症，调节炎症转录因子NF-κB和TNF-α的水平[17]；给自身免疫性脑脊髓炎动物灌胃25 mg/kg UA可降低疾病严重程度，通过过氧化物酶体增殖物激活受体γ（PPARγ）/CREB信号，激活少突胶质细胞成熟过程中髓鞘相关基因表达上调，诱导星形胶质细胞中促髓鞘生成神经营养因子[18]。

2.3 其他疾病中的抗炎作用

5 μmol/L UA通过抑制NF-κB/NLRP3炎症途径对TNF-α诱导的软骨细胞发挥抗炎作用，降低了细胞分解代谢酶和相关基因的表达，预防骨关节炎软骨退变[19]；变应性鼻炎大鼠灌胃20 mg/kg UA后可以产生免疫调节和抗炎作用减轻黏液分泌和组织重塑[20]；UA也可以通过干扰活性氧介导的细胞凋亡和光老化来减弱炎症反应以及紫外线诱导的细胞外损伤，从而成为一种潜在的保护皮肤的治疗药物[21]。

3 抗氧化作用

UA的抗氧化活性使它成为一种良好的自由基清除剂、链阻断抗氧化剂或自由基生成金属螯合剂，目前对UA的抗氧化潜能是比其他活性研究较少的[22]。糖尿病肾病大鼠灌胃35 mg/kg UA后可显著降低空腹血糖、肾脏重量、血液尿素氮、血清肌酐和丙二醛水平，而使SOD活性升高，说明UA可以通过抗氧化作用改善抗肾功能障碍[23]；SARAVANAN等[24]和LIN等[25]发现大鼠灌胃10、20、40 mg/kg UA后可以改善乙醇诱导的心脏异常，通过减少脂质过氧化过程和提高自由基清除酶以及增加还原型谷胱甘肽、抗坏血酸和α-生育酚等非酶抗氧化剂的水

平提高抗氧化能力，还可以通过 PERK-CHOP 途径减轻香烟烟雾诱导的肺细胞凋亡和肺氧化应激，从而改善大鼠肺气肿。用添加了 0.14% UA 的饲料饲喂 2 型糖尿病小鼠能够增加脂质 β 氧化和抑制肝脏内质网应激，从而降低小鼠的肝脏重量、血清 ALT/AST 水平和肝脏脂肪变性[26]。

4 抗癌作用

UA 主要通过抑制肿瘤发生和癌细胞增殖，调节凋亡，促进自噬等机制来发挥抗癌作用[27]。50 μmol/L UA 干预 LPS 诱导的小鼠胃肿瘤细胞和人胃癌细胞系（BGC-823 细胞）可以通过抑制 NF-κB 途径从而抑制癌细胞增殖[28]；用 160 μg/mL UA 干预乳腺癌细胞可以抑制细胞周期蛋白-D1 和刺激半胱氨酸天冬氨酸蛋白酶 3（caspase-3）引起癌细胞的凋亡和自噬，从而抑制乳腺癌的进展[29]；GUO 等[30]和 LIN 等[31]发现 0~20 μmol/L UA 可以降低宫颈癌 HeLa 细胞活力、诱导宫颈癌细胞凋亡和抑制口腔鳞状细胞癌（Oral squamous cell carcinoma，OSCC）细胞增殖及增加自噬小体积累，诱导 OSCC 细胞凋亡和自噬都具有时间和剂量依赖性[30-31]。

5 心脏保护作用

UA 可以通过保护心脏降低心血管疾病的发生和发展。心脏损伤小鼠皮下注射 UA 80 mg/kg 后增加了内皮型一氧化氮合酶（Endothelial nitric-oxide synthase，eNOS）的磷酸化水平，增强 eNOS 的表达，同时通过下调 NADPH 氧化酶 4（NADPH oxidase 4，NOX4）抑制阿霉素诱导的 eNOS 解偶联，改善了小鼠的左心室缩短和左心室射血分数，增加一氧化氮水平，抑制活性氧产生，减少心脏细胞凋亡[32]。皮下注射 80 mg/kg UA 后减轻了异丙肾上腺素诱导的大鼠心肌梗死的线粒体和溶酶体功能障碍[33]；还能够通过灌胃 35 mg/kg UA 减轻纤维化来改善链脲佐菌素诱导的糖尿病性心肌病大鼠的心脏结构和功能，并降低心肌组织中 TNF-α、单核细胞趋化蛋白-1 和转化生长因子-β1（Transforming growth factor-β，TGF-β1）的表达，上调基质金属蛋白酶-2（Matrix metalloproteinase，MMP-2）的表达[34]。

6 肝脏损伤保护作用

肝脏是体内代谢的主要器官，当肝脏受损会影响糖脂代谢，导致多种代谢性疾病发生。饲喂添加（0.125%、0.25%、0.5%）UA 的 HFD 可逆转 HFD 诱导的小鼠肝脂肪变性和肝损伤，上调肝脏过氧化物酶体增殖物激活受体（PPAR-a）的 mRNA 和蛋白水平，改善 HFD 诱导的脂质代谢紊乱[35]。UA 还可以通过调节肠道菌群来发挥保护肝脏作用，WAN 等[36]发现灌胃 40 mg/kg UA 可改善肝纤维化小鼠微生物群失调，通过抑制 NOX4/ROS 和 RhoA/ROCK1 信号通路逆转肝纤维化。灌胃 50~200 mg/kg UA 可以将 H22 肝癌细胞构建的移植瘤小鼠的肠道细菌菌群紊乱恢复到与对照组相似的程度，通过调节肠道菌群结构和数量，使其朝着正常组大鼠肠道菌群结构方向趋近，有效改善大鼠的酒精性肝损伤[37-39]。另外发现灌胃不同形态 20 mg/kg UA 均可以通过上调肝细胞生长因子的表达对肝再生有积极的作用[40]。

7 其他

UA 可以通过降低病毒滴度和主要病毒蛋白水平以及对病毒颗粒成熟的影响，10 μmol/L UA 干预后抑制了轮状病毒复制，阻碍病毒复制周期的早期阶段，病毒原体的数量和大小显著减少[41]；UA 具有潜在的抗弓形虫活性，灌胃 100 mg/kg UA 可有效恢复弓形虫感染小鼠的正常体质量，降低肝毒性，提高了弓形虫感染小鼠的生存时间[42]；UA 也被认为是一种潜在的治疗肌肉萎缩和保护骨骼的候选药物，包括骨骼肌萎缩、肌少症和肌肉代谢性疾病[43]；可以增加肌肉质量，减轻骨骼肌萎缩对骨骼健康的有害影响并且改善老年雌性大鼠骨骼特性和钙平衡，抑制破骨细胞分化[44-46]。

8 小结与展望

UA 来源十分广泛，随着人们对中草药的关注和重视，在许多常见中草药中发现了丰富的 UA 成分，且提取技术的不断提高是其开发利用的一大优势。近几年来，虽然熊果酸的降血脂、降血糖和保肝等作用都已有描述，但其作用的分子靶点和机制尚未明确阐明，相关活性分子的表达和功能的研究尚需进一步开展。探讨 UA 功能性作用机制为其未来作为新型的候选药物提供了科学依据。

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