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菝葜醇提物对小鼠脂肪代谢酶的影响

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摘要:【目的】研究菝葜醇提物(SCE)的成分及对小鼠体内脂肪代谢酶的影响。【方法】采用HPLC等方法分析SCE的成分组成。将50只雌性ICR小鼠随机分成5组,分别为对照组、高脂组、高脂添加0.25%、0.50%、1.00% SCE。投喂8周后,解剖,摘取小鼠的肝脏及腹腔内脂肪(IPAT)并称重。测定小鼠肝脏中肉毒碱转移酶(CAT)、酰基辅酶A氧化酶(ACO)、脂肪酸合成酶及磷酸腺苷激活蛋白激酶(AMPK)活性及mRNA表达量。【结果】SCE中的总多酚、总黄酮、总三萜的含量分别为:(42.54±0.45)%、(29.69±0.37)%、(14.03±0.21)%,其中落新妇苷、黄杞苷、绿原酸、白藜芦醇的含量分别是(23.65±0.36)mg/g、(7.97±0.03)mg/g、(13.65±0.19)mg/g、(7.46±0.15)mg/g。与高脂组相比,SCE喂养小鼠的体质量及体质量增加显著降低,0.50%及1.00% SCE明显减少IPAT质量。0.50%以上SCE的CAT、ACO、AMPK活性与高脂组相比显著提高。SCE明显上调CAT、ACO、AMPK的mRNA表达量。【结论】SCE中富含酚酸类化合物,可通过激活AMPK,促进脂肪酸氧化,减少脂肪沉积和体质量增加。

关键词:菝葜醇提物;成分分析;腹腔内脂肪;脂肪代谢酶

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Effects of *Smilax china* L. Ethanol Extract on Activities of Lipids Metabolism Related Enzymes in Mice

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Abstract: [Objective] This study aimed to investigate the constituent of *Smilax china* L. ethanol extract (SCE) and effects of SCE on lipid metabolism related enzymes in high-fat diet (HFD)-fed mice. [Method] The components of SCE were analyzed by colorimetric method and high performance liquid chromatography (HPLC). Then, fifty female ICR mice were randomly divided into 5 groups and fed with diets of control, HFD, HFD+0.25%, 0.50%, 1.00% SCE for 8 weeks. Liver and intraperitoneal adipose tissues (IPAT) were weighted at the end of this period. The activities of carnitine acyltransferase (CAT), acyl-CoA oxidase (ACO), fatty acid synthase and AMP-activated protein kinase (AMPK) and mRNA expression level were measured. [Results] The contents of total polyphenol, total flavonoids, total triterpenoid in SCE were (42.54±0.45)%, (29.69±0.37)%,

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and $(14.03 \pm 0.21)\%$, respectively. The contents of astilbin, engeletin, chlorogenic acid and resveratrol were (23.65 ± 0.36) mg/g, (7.97 ± 0.03) mg/g, (13.65 ± 0.19) mg/g and (7.46 ± 0.15) mg/g, respectively. Compared to HFD, body weight gain and IPAT were significantly reduced by the diets containing 0.50% and 1.00% SCE. Over 0.50% SCE markedly increased activities of CAT, ACO and AMPK. The mRNA expression levels of CAT, ACO and AMPK were markedly up-regulated by over 0.50% SCE. [Conclusion] These results showed the SCE is rich in polyphenols. It might induce activation of AMPK, increase activities of CAT and ACO, promote fatty acid β -oxidation, and cause the suppressive effect on fat accumulation and body weight gain in mice.

Keywords: *Smilax china* L. ethanol extract; component analysis; intraperitoneal adipose tissues; lipid metabolism related enzymes

【研究意义】肥胖是指一定程度的明显超重与脂肪层过厚,是体内中性脂肪过多积聚的表现。肥胖是一种典型慢性代谢疾病,它不仅影响人的体形,也与一些疾病有密切相关,如冠心病、高血压、2型糖尿病、高血脂等^[1-3]。随着国民生活水平不断提高,饮食习惯的日趋欧美化,我国肥胖症发病率呈逐年上升。因此,肥胖已经成为了一个国民关注的健康问题,预防与治疗也受到越来越多人的重视。目前,肥胖的治疗最常用的方法是服用化学合成的减肥药,长期服用不仅效果不理想,而且会对人体产生一定的副作用。因此,研究人员开始研究具备减肥功能且毒副作用低的天然产物,可通过日常饮食达到预防和治疗肥胖的效果。【前人研究进展】菝葜(*Smilax china* L.),百合科菝葜属植物,生长于海拔2 000 m以下的丘陵、河谷或山坡上,在我国的长江以南广泛分布^[4]。菝葜入药的历史悠久,古代医药书籍,如《名医别录》、《本草纲目》、《本草逢原》和《神农本草经疏》等书籍也都有记载。菝葜的全株均可入药,有疗疮痈肿,解毒散瘀祛风利湿等功效^[4]。从现代药理方面的研究证明菝葜有抗肿瘤、降血糖、抗炎、抑菌等效果^[5-7]。然而菝葜在减肥方面的研究还很少被报道。【本研究切入点】笔者用菝葜粉末喂养小鼠16周,发现菝葜粉末能显著的减少小鼠的体质量增加和腹腔内脂肪组织(IPAT)质量,表明菝葜具有一定的减肥降脂性能^[8]。但是菝葜什么组分有调节脂肪代谢还不清楚,其作用机制又如何?因此本研究通过乙醇提取菝葜,分析菝葜醇提物(SCE)中的活性物质,并将0.25%,0.50%和1.00%的SCE添加到饲料中投喂小鼠,测定小鼠体质量增加变化、IPAT质量、肝脏中脂类代谢相关酶的指标。【拟解决的关键问题】SCE降脂减肥作用有哪些组分构成,能否通过AMPK,促进脂类代谢,达到减肥作用。

1 材料与方法

1.1 动物及饲料

50只体质量约20 g雌性ICR小鼠(湖南斯莱克景达实验动物有限公司),许可证号:SCXK(湘)2011-0003。菝葜购于南昌药店(产地:安徽亳州市)。

饲料配制:SCE与高脂粉末饲料进行混合,配制成0.25%,0.50%和1.00% SCE混合饲料。

主要试剂:没食子酸、芦丁、薯蓣皂苷、绿原酸、白藜芦醇、落新妇苷、黄杞苷等标准品购自上海同田生物技术有限公司;小鼠酰基辅酶A氧化酶(ACO)、肉碱脂酰转移酶(CAT)、脂肪酸合成酶(FAS)、AMP激活蛋白激酶(AMPK)的ELISA试剂盒(北京索莱宝科技有限公司);ALLN、AEBSF、二硫苏糖醇、亮抑酶肽购自Sigma公司;其他试剂均为分析纯。

1.2 方法

1.2.1 菝葜醇提物的制备 菝葜磨粉,过60目筛,用60%的乙醇以1:20(Kg/L)的料液比浸泡1.5 h后,用超声提取机超声提取30 min,离心收集上清液,剩余沉淀再超声提取,合并两次收集的上清液,用真空旋转蒸发仪,温度在55℃下浓缩后,放入超低温冰箱冷冻,在冷冻干燥机中冷冻干燥,得到的SCE,装入自封袋,放在干燥器中保存。

1.2.2 菝葜醇提物的检测 (1)SCE的总三萜测定。称取薯蓣皂苷标准品,配成160 μ g/mL的工作液。用香草醛-冰醋酸法制作薯蓣皂苷标准曲线,具体参照文献^[9], $Y=0.108\ 1X+0.001\ 4$ ($R^2=0.998\ 6$),样品总

三萜含量根据该标准曲线进行计算。

(2)SCE的总多酚测定。称取没食子酸标准品,配成210 $\mu\text{g/mL}$ 的工作液。用福林酚试剂法绘制没食子酸标准曲线,具体参考文献^[9], $Y=0.086\ 1X+0.025$ ($R^2=0.999\ 6$),样品总多酚含量根据该标准曲线进行计算。

(3)SCE中总黄酮的测定。称取芦丁标准品,配成320 $\mu\text{g/mL}$ 的工作液,用硝酸铝法绘制没食子酸标准曲线,具体参考文献^[9], $Y=0.012\ 3X-0.003\ 3$ ($R^2=0.999\ 1$)样品总黄酮含量根据该标准曲线进行计算。

(4)SCE成分的HPLC测定。用Agilent 1260 Infinity 高效液相色谱仪分析SCE中的多酚成分含量。测定方法根据潘永芳^[9]进行。

1.2.3 动物饲养及解剖 50只雌性ICR小鼠适应性喂养7 d后,随机分成5组,对照组、高脂组、高脂添加0.25%、0.50%及1.00% SCE饲养8周,饲养期间自由采食和饮水,每周称量一次。饲养条件:室温(24 ± 2) $^{\circ}\text{C}$,光暗周期12/12(08:00—20:00)。8周后,小鼠禁食12 h以上,用乙醚麻醉后解剖,摘取肝脏、IPAT并称量,然后肝脏和IPAT放在 $-80\ ^{\circ}\text{C}$ 冰箱保存,直到分析为止。

1.2.4 肝脏脂肪代谢酶活性分析 肝脏匀浆参照潘永芳^[9]进行。

FAS、ACO、CAT和AMPK活性根据相应的ELISA试剂盒的使用说明书进行分析^[10]。

1.3 统计分析

实验数据采用以平均数 $\pm$ 标准误表示,用DPS统计软件(Version.6.55)进行 *student's t-test* 分析, $P<0.05$ 为差异显著。

2 结果

2.1 SCE主要成分及几种活性成分的含量

SCE中3种组分总三萜、总多酚、总黄酮的含量分别为(14.03 ± 0.21)%、(42.54 ± 0.45)%、(29.69 ± 0.37)%。SCE中的总多酚含量最高,达到42.54%。

图1显示混合标曲及SCE的HPLC图谱。经分析得,SCE中的绿原酸、落新妇苷、黄杞苷和白藜芦醇的含量分别为(13.65 ± 0.19) mg/g , (23.65 ± 0.36) mg/g , (7.97 ± 0.03) mg/g , (7.46 ± 0.15) mg/g 。

2.2 小鼠体质量、腹腔脂肪质量变化

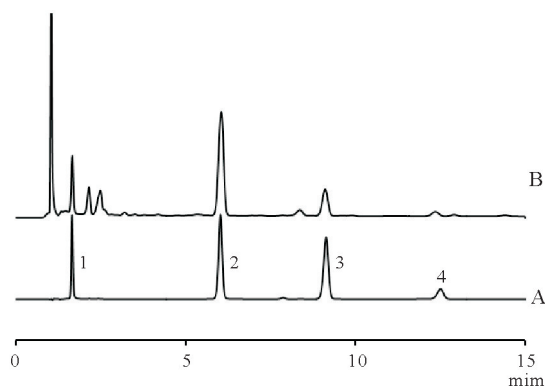
SCE对小鼠初始体质量、最终体质量、腹腔脂肪系数及肝脏系数的影响如表1所示。与高脂组相比,SCE投喂4周后,0.50%和1.00% SCE的小鼠体质量增加量显著减少。0.50%以上SCE投喂小鼠的腹腔脂肪系数明显低于高脂组。各组小鼠肝脏系数均无显著差异。综上可知,0.50%以上SCE可能主要是通过降低小鼠腹腔内脂肪沉积,减少体质量增加。

2.3 小鼠肝脏脂类代谢相关酶活性的变化

表2是SCE对小鼠肝脏中脂类代谢酶活性的影响。与高脂组相比,1.00% SCE投喂的小鼠肝脏中CAT和ACO活性显著提升,0.50%和1.00% SCE小鼠肝脏中AMPK活性明显提高。而各组小鼠FAS活性均无显著差异。

2.4 小鼠肝脏脂类代谢相关酶基因表达的变化

图2为SCE对小鼠肝脏及IPAT的脂类代谢相关酶基因表达的影响。与高脂组相比,1.00% SCE小鼠肝脏及IPAT中AMPK、CAT和ACO的mRNA表达量显著增加。而各组小鼠肝脏及IPAT中FAS活性均无显著差异。这些结果表明SCE增加小鼠的CAT、ACO和AMPK的基因表达量,并提高它们的活性,促进脂肪的氧化,减少脂肪沉积。



1:绿原酸;2:落新妇苷;3:黄杞苷;4:白藜芦醇
1: chlorogenic acid; 2: astilbin; 3: engeletin; 4: resveratrol
图1 混合标曲(A)与SCE(B)HPLC图谱
Fig.1 Chromatograms of standard mixture (A) and SCE (B)

表1 SCE对小鼠体质量、腹腔内脂肪及肝脏指数的影响

Tab.1 Effects of SCE on body weight,intraperitoneal adipose tissues(IPAT)and liver indexes in mice

	对照组 Control	HFD	HFD+0.25% SCE	HFD+0.50% SCE	HFD+1.00% SCE
初始体质量/g Initial body weight	21.98±0.37 ^a	22.77±0.43 ^a	22.48±0.53 ^a	22.41±0.59 ^a	21.84±0.46 ^a
最终体质量/g Final body weight	33.49±0.38 ^c	39.98±0.69 ^a	37.23±0.56 ^b	36.05±0.62 ^b	34.67±0.66 ^{bc}
体质量增加/g Body weight gain	11.51±0.40 ^c	17.21±0.79 ^a	14.75±0.76 ^b	13.64±0.74 ^b	12.83±0.82 ^{bc}
腹腔内脂肪指数(g/100g) IPAT index	3.95±0.36 ^c	5.34±0.54 ^a	4.88±0.42 ^{ab}	4.64±0.35 ^b	4.50±0.51 ^{bc}
肝脏指数(g/100g) Liver index	4.61±0.21 ^a	3.81±0.34 ^a	4.10±0.25 ^a	4.67±0.15 ^a	4.68±0.19 ^a

HFD:高脂组;SCE:菝葜醇提物;IPAT:腹腔内脂肪;数据以平均值±标准误表示,每组10只小鼠;同行肩标不同字母表示差异显著($P<0.05$)

HFD: high-fat diet, SCE: *Smilax china* L. ethanol extract, IPAT: intraperitoneal adipose tissues. Data is presented as mean±SE (n=10). Different letters on the same line indicated significant difference ($P<0.05$)

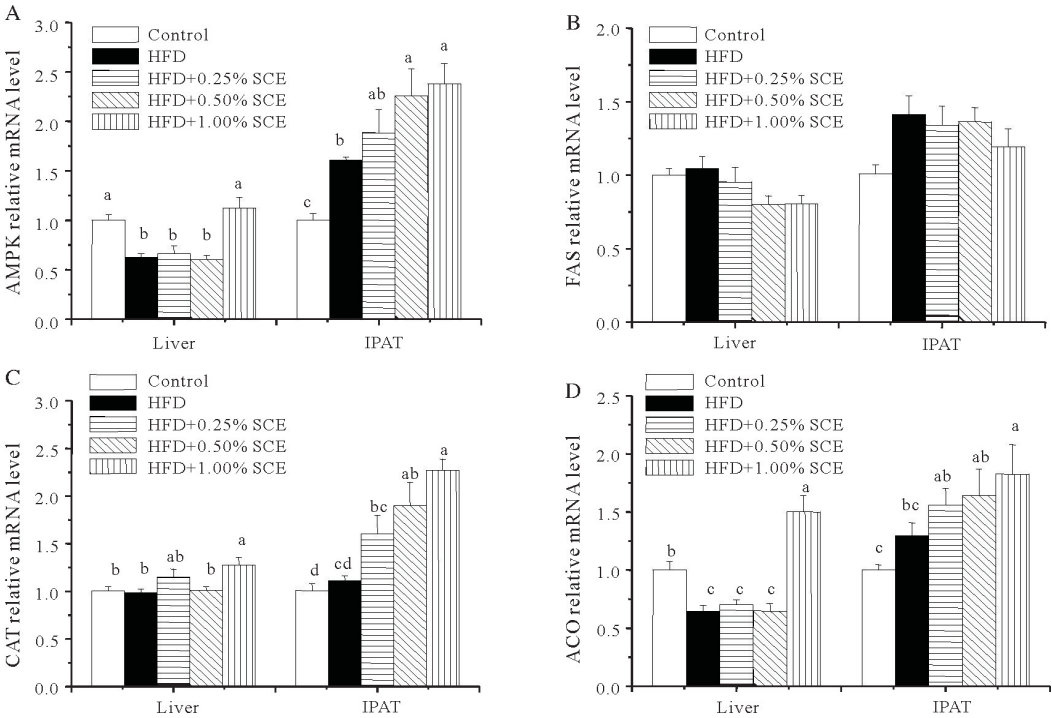
表2 SCE对小鼠肝脏中脂类代谢酶活性的影响(IU/mg 蛋白)

Tab.2 Effect of SCE on liver lipid metabolism related enzymes activity in mice(IU/mg protein)

	FAS	CAT	ACO	AMPK
对照组 Control	0.20±0.01 ^a	0.87±0.05 ^a	0.62±0.02 ^c	0.18±0.01 ^c
HFD	0.19±0.01 ^a	0.70±0.04 ^b	1.02±0.03 ^b	0.25±0.01 ^b
HFD+0.25% SCE	0.19±0.01 ^a	0.72±0.02 ^{ab}	0.96±0.07 ^b	0.30±0.01 ^{ab}
HFD+0.50% SCE	0.16±0.01 ^a	0.82±0.06 ^{ab}	1.07±0.05 ^b	0.32±0.03 ^a
HFD+1.00% SCE	0.18±0.01 ^a	0.89±0.05 ^a	1.43±0.02 ^a	0.33±0.02 ^a

HFD:高脂组;SCE:菝葜醇提物;FAS:脂肪酸合成酶;CAT:酯酰肉碱转移酶;ACO:酰基辅酶A氧化酶;AMPK:AMP激活蛋白激酶;数据以平均值±标准误表示,每组10只小鼠;同列肩标不同字母表示差异显著($P<0.05$)

HFD: high-fat diet, SCE: *Smilax china* L. ethanol extract, FAS: fatty acid synthase, CAT: Carnitine acyltransferase, ACO: acyl-CoA oxidase, AMPK: AMP-activated protein kinase. Data is presented as mean±SE (n=10). Different letters on the same column indicated significant difference ($P<0.05$)



HFD:高脂组;SCE:菝葜醇提物;FAS:脂肪酸合成酶;CAT:酯酰肉碱转移酶;ACO:酰基辅酶A氧化酶;AMPK:AMP激活蛋白激酶;数据以平均值±标准误表示,每组10只小鼠;肩标不同字母表示差异显著($P<0.05$)

HFD: high-fat diet, SCE: *Smilax china* L. ethanol extract, FAS: fatty acid synthase, CAT: Carnitine acyltransferase, ACO: acyl-CoA oxidase, AMPK: AMP-activated protein kinase. Data is presented as mean±SE (n=10). Different letters on the same column indicated significant difference ($P<0.05$)

图2 菝葜醇提物对小鼠肝脏中脂类代谢相关酶基因表达的影响

Fig.2 Effect of SCE on lipid metabolism genes expression in liver and IPAT of mice

3 讨论

前期实验中以2%、4%和8%的菝葜粉末投喂小鼠,发现4%以上菝葜明显减少小鼠的体质量增加和IPAT质量,表明菝葜有减肥功效^[8]。本研究0.50%以上的SCE有减少体质量增加和IPAT。通过分析SCE中主要组分,结果发现SCE中多酚含量较高,达到42.54%。有研究报道植物多酚对高脂诱导肥胖小鼠有减肥作用^[11]。因此,本研究SCE抑制体质量增加和IPAT质量可能是由于菝葜多酚类化合物引起的。

通过分析SCE对肝脏和IPAT中脂类代谢酶的影响,发现SCE喂养的小鼠中CAT、ACO和AMPK的酶活性及基因表达量显著提升。研究显示苦瓜通过激活肝脏和肌肉的CAT酶的活性,增加脂肪氧化,减少大鼠体内脂肪积累^[12]。研究表明上调小鼠肝脏中AMPK的基因表达,从而促进ACO、CAT的mRNA表达,提升ACO和CAT的活性,抑制脂肪沉积,减少体质量增加^[13-14]。在本试验中,0.50%以上的SCE显著增加小鼠肝脏中ACO及CAT的活性及mRNA表达量,从而促进小鼠体内的脂肪酸 β -氧化,减少脂肪沉积。

AMPK是一个重要的蛋白激酶,能调节机体的代谢和能量需求,在调控体内能量代谢中起着非常重要的作用^[15]。激活AMPK抑制合成代谢,促进分解代谢途径开启,是体内主要的能量传感器^[16]。研究表明,激活AMPK提高HSL活性,促进脂肪分解代谢^[17];增加ATGL蛋白表达水平,抑制体内脂肪积累^[18];抑制细胞葡萄糖摄入和脂肪合成^[19]。激活AMPK促进磷酸化ACC和HMG-CoAR,抑制它们活性,从而减少脂肪酸和胆固醇的合成^[20,21]。有研究报道用黄连素喂养小鼠,发现小鼠肝脏质量减少,血清和肝脏中脂类含量降低,预防肥胖效果,这些结果表明黄连素可以通过激活AMPK来达到减肥作用^[22]。二甲双胍(一种降糖药剂)能提高胰岛素敏感性的同时,还能通过激活AMPK促进机体能量代谢、减少脂肪积累,抑制体质量增加^[23]。AMPK的激活还可以通过上调CAT的基因和蛋白表达来促进脂肪酸的氧化^[24]。因此,AMPK的激活可调控脂类代谢相关酶的基因和蛋白表达。

综上所述,本研究结果表明SCE减肥作用可能是由菝葜多酚类化合物引起的,其通过提升AMPK mRNA的表达量,调节小鼠肝脏和脂肪组织中的CAT和ACO的活性及基因表达水平,促进脂肪氧化,从而减少小鼠体内脂肪蓄积,降低体质量增加。

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