

黃梔子萃出物對血糖及胰島素敏感性影響之探討

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摘要

糖尿病是一種因胰島素分泌或胰島素作用缺陷而影響糖、脂肪及蛋白質的代謝紊亂所照成的代謝疾病。目前世界衛生組織衛生組織將糖尿病分為三類：第1型糖尿病、第2型糖尿病、妊娠型糖尿病，其中第2型糖尿病患者占90%。胰島素阻抗是導致第二型糖尿病的主要因素。胰島素阻抗是指在正常的胰島素濃度不能與脂肪、肌肉和肝臟等組織產生正常胰島素的反應，也就是組織對於胰島素的敏感性降低。黃梔子在過去文獻已提出具有降血糖、降胰島素及降血脂等改善糖尿病活性，但其機制尚未完全清楚，本研究首先利用正常大鼠餵食不同濃度黃梔子萃出物以尋找降血糖的最佳劑量，並運用在經由類固醇誘發的胰島素阻抗大鼠上，觀察是否也具有降血糖的效果。接著在類固醇誘發的胰島素阻抗大鼠上，評估其改善胰島素敏感性的效果，最後檢測血中游離脂肪酸，探討黃梔子萃出物藉由影響血中游離脂肪酸來達到改善胰島素敏感性的效果。結果顯示：黃梔子萃出物在正常大鼠表現出降血糖的效果，且在餵食濃度200 mg/kg時有較佳的降糖率。且在類固醇誘發的胰島素阻抗大鼠也有顯著降低血糖的效果。而在胰島素增敏評估中，發現黃梔子萃出物具有增加胰島素敏感度的表現，但血中游離脂肪酸的改變未達統計顯著差異，可能黃梔子萃出物增加胰島素敏感度的作用，不是藉由降低血中游離脂肪酸達到效果，但可能因為餵食的時間較短，故無法顯現效果，必須進一步的研究，才能明確表示黃梔子對於游離脂肪酸的影響。結論：本研究發現黃梔子萃出物在餵食濃度200 mg/kg時，具有顯著的降糖效果並且能改善類固醇誘發胰島素阻抗大鼠的高血糖症狀，以及增加胰島素敏感度，藉此能提供未來發展黃梔子做為胰島素增敏劑的方向。

關鍵詞：糖尿病、血糖、胰島素、游離脂肪酸、胰島素阻抗、黃梔子

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參考文獻

- 1.于洋。2010。黃梔子屬植物化學成分的研究進展。中草藥41(1)。
- 2.王德震。2008。消渴病病因病機理論與臨床研究述略。實用中醫內科雜誌22(11): 2。
- 3.付田。2007。黃梔子京尼平?對小鼠急性酒精性肝損傷的保護作用。中藥藥理與臨床23(3)。
- 4.田德祿。2005。中醫內科學: 中國中醫藥出版社。
- 5.白蕙菁。2007。電針並用胰島素增敏劑對第2型糖尿病影響之探討。中國醫藥大學碩士論文。台中市。
- 6.石若夫。2002。黃梔子多糖的抗腫瘤活性研究。林產化學與工業22(4)。
- 7.行政院衛生署。民國90年國人主要死因統計資料。
- 8.林榮宗。2005。電針改善類固醇誘導胰島素阻抗大鼠之研究。中國醫藥大學碩士論文。台中市。
- 9.邱永年, 張光雄。1986。原色臺灣藥用植物圖鑑(2)。第213-214頁。南天書局。
- 10.姜德友, 林?。2007。消渴病源流考。遼寧中醫雜誌。34(10): 1373-1375。
- 11.?泰康。1994。常用中藥成分與藥理手冊: 中國醫藥科技出版社。
- 12.董婉茹。2011。黃梔子在治療肝臟疾病中的研究進展。中國實驗方劑學雜誌。17(23)。
- 13.鄭虎占, 董澤宏, 余靖。1998。中藥現代研究與應用(第四卷)。第3166頁。學苑出版社。
- 14.鄭婷宜。2001。利用微透析技術探討針灸對黃梔子?藥物動力學的影響以及黃梔子相關藥材分析。國立陽明大學碩士論文。台北市。
- 15.顏焜熒。1992。原色生藥學。第109-110頁。南天書局。
- 16.Bjornholm, M., Kawano, Y., Lehtihet, M., & Zierath, J. R. 1997. Insulin receptor substrate-1 phosphorylation and phosphatidylinositol 3- kinase activity in skeletal muscle from NIDDM subjects after in vivo insulin stimulation. Diabetes, 46(3): 524-527.

17. Bloomgarden, & Zachary, T. 2006. Measures of insulin sensitivity. Philadelphia, PA, ETATS-UNIS: Elsevier. 18. Bogardus, C., Lillioja, S., Mott, D. M., Hollenbeck, C., & Reaven, G. 1985. Relationship between degree of obesity and in vivo insulin action in man. *American Journal of Physiology - Endocrinology And Metabolism*, 248(3): E286-E291. 19. Casey, A. 2004. Hormonal control of metabolism: regulation of plasma glucose. *Anaesthesia & Intensive Care Medicine*, 5(7): 240-243. 20. DeFronzo, R. A., & Ferrannini, E. 1991. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*, 14(3): 173-194. 21. Ganong, W. F. 2001. Review Of Medical Physiology: McGraw-Hill Medical Co. 22. Griffin, M. E., Marcucci, M. J., Cline, G. W., Bell, K., Barucci, N., Lee, D., Goodyear, L. J., Kraegen, E. W., White, M. F., & Shulman, G. I. 1999. Free fatty acid-induced insulin resistance is associated with activation of protein kinase C theta and alterations in the insulin signaling cascade. *Diabetes*, 48(6): 1270-1274. 23. Grundy, S. M., Brewer Jr, H. B., Cleeman, J. I., Smith Jr, S. C., & Lenfant, C. 2004. Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation*, 109(3): 433-438. 24. Guyton, A. C., & Hall, J. E. 1996. Textbook Of Medical Physiology: W.B. Saunders Co. 25. Heydari, I., Radi, V., Razmjou, S., & Amiri, A. 2010. Chronic complications of diabetes mellitus in newly diagnosed patients. *International Journal of Diabetes Mellitus*, 2(1): 61-63. 26. Huang, S., & Czech, M. P. 2007. The GLUT4 Glucose Transporter. *Cell metabolism*, 5(4): 237-252. 27. Itani, S. I., Zhou, Q., Pories, W. J., MacDonald, K. G., & Dohm, G. L. 2000. Involvement of protein kinase C in human skeletal muscle insulin resistance and obesity. *Diabetes*, 49(8): 1353-1358. 28. Jang, S.-M., M.-J. Kim, (2010). "Inhibitory effects of ursolic acid on hepatic polyol pathway and glucose production in streptozotocin-induced diabetic mice." *Metabolism* 59(4): 512-519. 29. JR, G., KGMM, A., MB, D., RA, D., A, D., & SG, G. 1997. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*, 20: 1183 – 1197. 30. Kaplan, N. M. 1989. The Deadly Quartet: Upper-Body Obesity, Glucose Intolerance, Hypertriglyceridemia, and Hypertension. *Arch Intern Med*, 149(7): 1514-1520. 31. Kimura, Y., Okuda, H., & Arichi, S. 1982. Effects of Geniposide isolated from *Gardenia jasminoides* on Metabolic Alterations in High Sugar Diet-fed Rats. *Chemical & pharmaceutical bulletin*, 30(12): 4444-4447. 32. Kojima, K., Shimada, T., Nagareda, Y., Watanabe, M., Ishizaki, J., Sai, Y., Miyamoto, K.-i., & Aburada, M. 2011. Preventive Effect of Geniposide on Metabolic Disease Status in Spontaneously Obese Type 2 Diabetic Mice and Free Fatty Acid-Treated HepG2 Cells. *Biological and Pharmaceutical Bulletin*, 34(10): 1613-1618. 33. Koo, H.-J., Song, Y. S., Kim, H.-J., Lee, Y.-H., Hong, S.-M., Kim, S.-J., Kim, B.-C., Jin, C., Lim, C.-J., & Park, E.-H. 2004. Antiinflammatory effects of genipin, an active principle of gardenia. *European Journal of Pharmacology*, 495(2-3): 201-208. 34. Kovacs, P., & Stumvoll, M. 2005. Fatty acids and insulin resistance in muscle and liver. *Best Practice & Research Clinical Endocrinology & Metabolism*, 19(4): 625-635. 35. Liaw, J., & Chao, Y.-C. 2001. Effect of in vitro and in vivo aerosolized treatment with geniposide on tracheal permeability in ovalbumin-induced guinea pigs. *European Journal of Pharmacology*, 433(1): 115-121. 36. Liu, S., & Manson, J. E. 2001. Dietary carbohydrates, physical inactivity, obesity, and the 'metabolic syndrome' as predictors of coronary heart disease. *Curr Opin Lipidol*, 12(4): 395-404. 37. Marble, A. 1976. Late complications of diabetes. A continuing challenge. The Elliott P. Joslin Memorial Lecture of the German Diabetes Federation. *Diabetologia*, 12(3): 193-199. 38. Matthews, R., D., Hosker, P., J., RUDENSKI, S., A., NAYLOR, A., B., TREACHER, F., D., TURNER, & C., R. 1985. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. Heidelberg, ALLEMAGNE: Springer. 39. Meshkani, R., & Adeli, K. 2009. Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. *Clinical Biochemistry*, 42(13 – 14): 1331-1346. 40. Meshkani, R., Taghikhani, M., Larijani, B., Khatami, S., Khoshbin, E., & Adeli, K. 2006. The relationship between homeostasis model assessment and cardiovascular risk factors in Iranian subjects with normal fasting glucose and normal glucose tolerance. *Clinica Chimica Acta*, 371(1 – 2): 169-175. 41. Melo, C. L., Queiroz, M. G. R., Fonseca, S. G. C., Bizerra, A. M. C., Lemos, T. L. G., Melo, T. S., Santos, F. A., & Rao, V. S. 2010. Oleonic acid, a natural triterpenoid improves blood glucose tolerance in normal mice and ameliorates visceral obesity in mice fed a high-fat diet. *Chemico-Biological Interactions*, 185(1): 59-65. 42. Oghihara, T., Asano, T., & Fujita, T. 2003. Contribution of salt intake to insulin resistance associated with hypertension. *Life Sciences*, 73(5): 509-523. 43. Petersen, K., Bramsiepe, N., & Pohl, K. 2006. Applying variability modeling concepts to support decision making for service composition. 44. Randle, P. J., Garland, P. B., Hales, C. N., & Newsholme, E. A. 1963. THE GLUCOSE FATTY-ACID CYCLE ITS ROLE IN INSULIN SENSITIVITY AND THE METABOLIC DISTURBANCES OF DIABETES MELLITUS. *The Lancet*, 281(7285): 785-789. 45. Ryan, A. S. 2000. Insulin resistance with aging: effects of diet and exercise. *Sports Med*, 30(5): 327-346. 46. Saad, M. J., Folli, F., Kahn, J. A., & Kahn, C. R. 1993. Modulation of insulin receptor, insulin receptor substrate-1, and phosphatidylinositol 3-kinase in liver and muscle of dexamethasone-treated rats. *The Journal of Clinical Investigation*, 92(4): 2065-2072. 47. Sarbassov, D. D., Guertin, D. A., Ali, S. M., & Sabatini, D. M. 2005. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. *Science*, 307(5712): 1098-1101. 48. Sheng, L., Qian, Z., Zheng, S., & Xi, L. 2006. Mechanism of hypolipidemic effect of crocin in rats: Crocin inhibits pancreatic lipase. *European Journal of Pharmacology*, 543(1-3): 116-122. 49. Shoelson, S. E., Herrero, L., & Naaz, A. 2007. Obesity, Inflammation, and Insulin Resistance. *Gastroenterology*, 132(6): 2169-2180. 50. Suzuki, Y., Kondo, K., Ikeda, Y., & Umemura, K. 2001. Antithrombotic effect of geniposide and genipin in the mouse thrombolysis model. *Planta Med*, 67(9): 807-810. 51. Thong, F. S. L., Dugani, C. B., & Klip, A. 2005. Turning Signals On and Off: GLUT4 Traffic in the Insulin-Signaling Highway. *Physiology*, 20(4): 271-284. 52. Thorens, H.-G. J., Bernard. 2001. The extended GLUT-family of sugar/polyol transport facilitators: nomenclature, sequence characteristics, and potential function of its novel members. *Molecular Membrane Biology*, 18(4): 247-256. 53. Tseng, T.-Y., & Tsai, T.-H. 2004. Measurement of unbound geniposide in blood, liver, brain and bile of anesthetized rats: an application of pharmacokinetic study and its influence on acupuncture. *Analytica Chimica Acta*, 517(1-2): 47-52. 54. Vanhaesebroeck, B., & Alessi, D. R. 2000. The PI3K-PKB1 connection: More than just a road to PKB. *Biochemical Journal*, 346(3): 561-576.

55. World Health Organization. 2011. Diabetes, Fact sheet N ° 312. 56. Wu, S.-y., Wang, G.-f., Liu, Z.-q., Rao, J.-j., Lu, L., Xu, W., Wu, S.-g., & Zhang, J.-j. 2009. Effect of geniposide, a hypoglycemic glucoside, on hepatic regulating enzymes in diabetic mice induced by a high-fat diet and streptozotocin. *Acta Pharmacol Sin*, 30(2): 202-208. 57. Zhang, C.-Y., Parton, L. E., Ye, C. P., Krauss, S., Shen, R., Lin, C.-T., Porco, J. A., & Lowell, B. B. 2006. Genipin inhibits UCP2-mediated proton leak and acutely reverses obesity- and high glucose-induced β cell dysfunction in isolated pancreatic islets. *Cell metabolism*, 3(6): 417-427.