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厦门大学

硕　士　学　位　论　文

绿原酸-栀子苷组合调控非酒精性脂肪性肝病剂量配比优化研究

Optimazation Dosage Study of the Combination of Chlorogenic and Geniposide on Non-alcoholic Fatty Liver Disease

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摘 要

目的：本研究通过运用数学模型均匀设计法，观察中药有效成分绿原酸、栀子苷配伍使用对高脂饮食诱导非酒精性脂肪性肝病（NAFLD）大鼠模型所产生的药理效应。并从多角度指标分析绿原酸、栀子苷对 NAFLD 脂质代谢紊乱、肝脏炎症损伤病理状态的影响，筛选出绿原酸-栀子苷组合抗 NAFLD 的最优剂量配比，探索中药复方治疗 NAFLD 的药效基础。

方法：1、均匀设计筛选实验：55 只雄性 Wistar 大鼠，随机分为正常组、造模组。正常组普通饲料喂养，造模组采用改良高脂饲料饮食 8 周诱导 NAFLD 大鼠模型。造模组自第 5 周开始随机分为模型组和 6 组药物组。药物组以绿原酸、栀子苷作为考察因子，选用 U^6（6^4）均匀表进行组方设计，所得 6 组绿原酸-栀子苷组合水平为各药组所对应 100g 大鼠每日给药量。4 周用药结束后，观察记录各组大鼠一般情况（体重、肝湿重、脂肪重量、肝指数），并检测脂质代谢（肝组织 TG、血清 CHO、LDL-C、HDL-C）、炎症损伤（血清 ALT、AST）等相关指标。采用多元逐步回归方法分析针对不同指标的效应成分，筛选出抗 NAFLD 的绿原酸-栀子苷组合最优剂量配比。

2、验证实验：根据筛选实验综合分析所得绿原酸-栀子苷最优配比组合，并设正常组、模型组、绿原酸组、栀子苷组、血脂康组、绿原酸-栀子苷最佳剂量配比组进行对比，再次使用上述方法造模，以验证观察实验结果，观察指标同筛选实验。

结果：1、均匀设计筛选实验：模型组大鼠体重、肝湿重、脂肪重量、肝指数、肝组织 TG、血清 CHO、LDL-C、ALT、AST 均较正常组大鼠升高，血清 HDL-C 较正常组降低（$P<0.05$），提示高脂饮食诱导 NAFLD 模型成功。药物组各指标较模型组有不同程度改善，经优化指标综合分析筛选得出最佳剂量配比为绿原酸、栀子苷各 90mg。

2、验证实验：与模型组比较，绿原酸-栀子苷最优剂量配比组可显著降低 NAFLD 大鼠模型肝组织 TG、血清 CHO、LDL-C 水平，升高血清 HDL-C 水平，降低血清 ALT、AST 活性，改善 NAS 活动积分（$P<0.05$）。与其它治疗组比较，

最优剂量配比组肝组织病理学结果优于绿原酸组、栀子苷组与血脂康组；降低模型体重、脂肪重量优于绿原酸组、血脂康组；降低肝指数优于栀子苷组；降低血清 CHO 水平优于血脂康组；降低血清 ALT 活性优于绿原酸组；NAS 积分明显低于绿原酸组（$P<0.05$）；

结论：1、通过改良后的高脂饮食，可以成功诱导NAFLD大鼠模型。

2、运用数学模型均匀设计法可以较准确地优化中药复方中两个以上有效成分的剂量配比。

3、中药有效成分绿原酸、栀子苷配伍使用具有降低肝组织TG、血清CHO、LDL-C水平，降低血清ALT、AST活性，提高血清HDL-C水平的药理效应，两种中药有效成分在调节以上指标中具有明显的交互效应，其最优剂量配比为绿原酸、栀子苷各90mg。

4、经均匀设计法筛选出的绿原酸-栀子苷组合最优剂量配比，能有效地改善高脂饮食诱导NAFLD大鼠模型脂质代谢异常和炎症损伤的病理状态，其综合药理学效应较单独应用同等剂量绿原酸组、栀子苷与常规剂量的血脂康更为明显。

关键词：非酒精性脂肪性肝病　均匀设计法　绿原酸　栀子苷　绿原酸-栀子苷组合

Abstract

Objective: To observe the effects of the combination of chlorogenic acid and geniposide, which are effective components of Chinese medicine, on experimental rat model of Non-alcoholic fatty liver disease （NAFLD）induced by high fat diet, we applied uniform design method to establish the the mathematical model. What's more, we chose muti-angle indexs to analyse the effects of chlorogenic acid and geniposide on the lipid metabolism and inflammation injury of NAFLD , in order to screen the optimal dosage propotion of the combination of chlorogenic acid and geniposide. By these meseures above, we hope to find the pharmacodynamics basis of prescription of Chinese medicine realated to NAFLD.

Methods: 1.Uniform design screening experiment:55 male Wistar rats were randomly divide into nomal group and model group. Normal group were fed with nomal fodder during all the experiment. Meanwhile, model group were fed with improved high fat diet for 8 weeks and divided into original model group and 6 treatment groups at the begining of 5th week. We arranged 6 levels of combination of chlorogenic acid and geniposide as the daily dosage per 100 grams of rat weights on 6 teatment groups, accroding to the table $U_6(6^4)$ of uniform design. After the rats were killed, their body weight, liver weight, fat weight and liver index were recorded. Furthermore, their blood an livers were collected for research. The indexes which need to test including:levels of liver TG, serum CHO, LDL-C, HDL-C and activities of serum ALT,AST. All the indexes above were analyzed by mutiple stepwise regression to sreen the optimal dosage proportion of the combination of chlorogenic acid and geniposide to treat NAFLD.

2. Verification experiment: To verify the optimal dosage proportion of the combination of chlorogenic acid and geniposide to treat NAFLD from screening expriment, we establish the rats model of NAFLD as before. And buliding the normal group, model group, chlorogenic acid group, geniposide group and Xuezhikang group

to compare the therapeutic effect with the optimal dose propotion.Testing indexes are same as screening experiment.

Results:1. Uniform design screening experiment: In comparison with the normal group, the model group's body weight, liver weight, fat weight, liver index, levels of liver TG, serum CHO,LDL-C, ALT, AST are increased significantly, and serum HDL-C are decreased significantly($P<0.05$). It implied the model of NAFLD is sucessful. In comparison with model group, the indexes of 6 treatment groups imoprved more or less. By comprehensive analysis of every index, the optimal dosage propotion is 90mg chlorogenic acid and 90mg geniposide.

2. Verification experiment: In comparison of model group, the optimal dose propotion group can obviously improve the indexes of liver TG,serum CHO,LDL-C, HDL-C, ALT, AST and NAS($P<0.05$). In comparison of other teatment groups, the optimal dosage propotion group has a better liver tissue pathological results, which is better than chlorogenic acid group and Xuezhikang group in body weight and fat weight as well. Moreover, the optimal dosage proportion group decresed more significantly in liver index than geniposide group, while it also has a superiority in decresing more in serum CHO than Xuezhikang group, which is also better than both reducing the activity of serum ALT and NAS in chlorogenic acid group($P<0.05$).

Conclusions:1. Improved high fat diet can induce rat model of NAFLD sucessfully.

2. Mathmatical model of uniform design can screen the optimal dose proportion of two or more effective components of Chinese medicine prescription.

3. The combination of chlorogenic acid and geniposide has a significant pharmacological effect of decreasing levels of liver TG, serum CHO,LDL-C, activities of serum ALT,AST and increasing level of serum HDL-C.Besides, there has a outstanding interaction in the above indexes. The optimal dosage proportion is 90mg chlorogenic acid and 90mg geniposide.

4. The optimal dosage proportion of chlorogenic acid and geniposide, from uniform design screening, has a significant pharmacological effect on rat model of NAFLD inuduced by high fat diet. It can availably improve the pathological state of

NAFLD,especilally in the field of lipid metabolism and inflammation injury .Meanwhile, its comprehensive pharmacological effect is superior to separate chlorogenic acid group, separate geniposide group or Xuezhikang group.

Keywords: Non-alcoholic fatty liver disease; Uniform design; Chlorogenic acid; Geniposide; The combination of Chlorogenic acid and geniposide

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