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Hypoglycemic Effect of Ampelopsin on Diabetic Rats Induced by Steptozotocin
双氢杨梅树皮素对链脲霉素所致糖尿病大鼠的降糖作用*

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Abstract For studying the mechanism of ampelopsin hypoglycemic effect, fifty SD strain male rats with diabetic models induced by steptozotocin (STZ) were treated with ampelopsin (AP) for 30 days. The results showed that AP could lighten hyperglycemic reaction, increase the SOD-cu. zn activity and decrease the MDA contents; triglyceride (TG) in blood-lipid had lowering tendency and raised insulin levels in serum. Histological examination showed that pancreatic island number in pancreas in AP groups increased in compared with the model group, reducing lymphocyte infiltration and lightening inflammatory. It's mechanism might be of lightening the β-cell injuring of pancreatic island induced by STZ or promoting the reparation of injured β-cells, and enhancing the secreted function of pancreatic island cells through the anti-oxidation of AP, thus lowering blood sugar level in diabetic rats.

Key words ampelopsin, hypoglycemic, lipid-lowering, anti-oxidation, animal experiment

摘要 用链脲霉素 (STZ) 所致的大鼠糖尿病作模型, 给予双氢杨梅树皮素 (AP) 连续治疗 30 d, 探讨 AP的降糖作用机理。结果表明: AP能使 STZ糖尿病大鼠的高血糖反应减轻,增加血清中 SOD-cu. zn活性,降低 MDA含量, 对血脂中的甘油三酯 (TG) 水平有降低趋势; 可提高血清中胰岛素水平。组织学研究可见 AP组大鼠胰腺组织中的胰岛数目较模型组增多,淋巴细胞浸润减少,炎症反应减轻。其作用机理可能是通过 AP的抗氧化作用, 减轻 STZ对胰岛β细胞损伤, 或促进已损伤的β细胞的修复, 增强胰岛细胞的分泌功能, 起到降低血糖的作用。

关键词 双氢杨梅树皮素 降血糖 降血脂 抗氧化 动物实验
中图法分类号 R 962

Ampelopsin (AP), extracted from the tender stem and leaves of *Ampelopsis grossedentata* (Hand-Mazz) W. T. wang, is one of total flavone components in this plant. It could relieve a cough and remove sputum action[1], and has hypoglycemic effect in diabetic rats induced by alloxin. In this paper, we observed the pharmacologic effects of AP on bood sugar, blood-lipid, SOD, MDA and insulin in diabetic rats induced by steptozotocin (STZ).

1 Materials and Methods

1.1 Drugs and Reagents

AP, a kind of yellow-white powder crystals, was provided by the Pharmacy Department of Guangxi College of Chinese Traditional Medicine. The suspension was prepared by grinding AP together with a few drops of Tween-80(Polysorbate 80) when used. Xiaokewan (XKW) was from the First Pharmaceutical Factory of Traditional Chinese Medicine of Guangzhou, batch number 9806441; Steptozotocin (STZ) from Sigma Co.; 0.5% STZ solution was prepared with 0.1 mol/L citric acid and sodium citric acid buffers (pH4.2) before use. Both kits of serum glucose (GLU), total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL-C) were from Dongou Biol Engin Co.. Both the kits of superoxide dismutase (SOD) and malindialdehyde (MDA) were from Jiancheng Institute of Biol. Engin. in Nanjing; insulin radioimmunoassay kit from Chinese Institute of Atomic Energy Isotope, batch number 199907.

1.2 Animals

Fifty SD strain male rats, weighing 180 g~ 220

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g, were provided by the Animal Department of Guangxi Institute of Traditional Medical and Pharmaceutical Sciences.

1.3 Instruments

Grating spectrophotometer(model 722) was made by Shanghai Analytical Instrument Third Factory. Radioimmunity r-detector (SN-695A) by the Rihuan Instrument First Factory of Shanghai Institute of Atomic Energy.

1.4 Diabetic rats induced by STZ

By methods in references [2, 3], Fifty male rats were used, in which ten were chosed out randomly as control, the rest were intraperitoneally injected with 0.5% STZ solution at the dose of 50 mg/kg weights. 72 hours after injection, the blood samples were collected from tail vein in the fasted rats, and the levels of serum glucose and insulin were determined. The serum glucose level of over 16 mmol/L was defined as diabetic model rats, then those rats were divided into 4 groups of model, XKW, high and low dose of AP. The rats were orally administered once a day for 30 days with the drugs and doses shown in Table 1. The rats were anesthetized with sodium pentobarbital (40 mg/kg) at 24 hour after last administration. The indexes of serum glucose, lipid, insulin, SOD and MDA were determined with the blood samples collected from abdominal aorta. The rats were killed immediately, their pancreas were taken out and fixed with 10% formalin, and cut into sections and HE dying by ordinary method. Histologic examination was performed under optic microscope.

1.5 Detecting indexes

The serum glucose was determined by method of glucose oxydase, total cholesterol (TC), triglyceride (TG); high density lipoprotein (HDL-C) by enzyme methods; SOD-cu. zu activity by xanthinoxidase method; MDA content by thiobarbituric acid; serum insulin by radioimmunoassay method. When the shape and size of pancreatic island in pancreas tissue were observed by histologic method, and average number of pancreatic island was counted using the standard of ten vision fields in the pathologic section of each case under low-powered microscope, and the cell number in pancreatic island was counted under high-powered microscope.

2 Result

2.1 Effect of AP on blood sugar levels of diabetic rats induced by STZ

The results were shown in Table 1. Comparing with model group, both high and low dose groups of AP could significantly lowered blood sugar levels ($P < 0.05$), and high dose group was similar to XKW (as positive drug) in action. The results showed that AP has significant hyperglycemic effect on diabetic rats induced by STZ.

Table 1 Effect of AP on blood sugar levels of diabetic rats induced by STZ ($\bar{x} \pm s$)

Group	Doses (g/kg)	Animal number	Blood sugar (mmol/L)		
			Before p.o	30 d after p.o	Decreased rate (%)
Control		10	5.49± 0.98	5.74± 0.55	
Model		10	26.04± 8.39	21.29± 4.64	
XKW	2.5	10	24.42± 7.67	15.99± 6.85	24.9
AP	0.25	10	25.32± 9.30	15.50± 6.63*	27.2
AP	0.125	10	25.15± 8.99	17.62± 3.52	17.2

Compared with model group* $P < 0.05$.

2.2 Effect of AP on blood lipid levels

The results were shown in Table 2. After oral administration of AP for 30 days in diabetic rats induced by STZ, no influencing TC and HDL-C contents were showed, but TG levels exhibits significant lower. The results suggest that AP has definite lipid-lowering effect on diabetic rats induced by STZ.

Table 2 Effect of AP on lipid levels in diabetic rats induced by STZ ($\bar{x} \pm s$, $n = 10$)

Group	Doses (g/kg)	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)
Control		2.19± 0.55	0.48± 0.16	1.26± 0.28
Model		2.20± 0.39	1.20± 0.55	1.16± 0.19
XKW	2.5	2.17± 0.48	0.71± 0.26*	1.16± 0.27
AP	0.25	2.08± 0.34	0.75± 0.31*	1.22± 0.19
AP	0.125	2.37± 0.32	0.90± 0.13	1.22± 0.22

Compared with model group* $P < 0.05$.

2.3 Effect of AP on the SOD activity and MDA content in serum of diabetic rats induced by STZ

The results were shown in Table 3. The SOD activity in serum of diabetic rats had increasing effect, while MDA contents exhibited significant lowering effect, and the high dose group of AP was similar to XKW in effect after oral given for 30 days. The results suggest that AP has better anti-oxidation.

Table 3 Effect of AP on the SOD activity and MDA content in serum of diabetic rats induced by STZ ($\bar{x} \pm s$)

Group	Doses (g/kg)	n	SOD (NU/ml)	MDA (nmol/ml)
Control		10	102.4± 34.2	7.5± 1.2
Model		10	89.4± 11.9△△	11.4± 1.8△△
XKW	2.5	10	117.7± 20.0**	9.1± 1.6**
AP	0.25	10	111.5± 24.3**	8.6± 1.4**
AP	0.125	10	104.4± 13.3*	9.4± 1.2*

Compared with model group* $P < 0.05$, ** $P < 0.01$. Compared with control group△△ $P < 0.01$.

2.4 Effect of AP on the insulin levels in serum of diabetic rats induced by STZ

The results were shown Table 4. The insulin

levels were significant lowering before oral given in diabetic rats induced by STZ. Comparing with model group, insulin levels in high and low dose groups of AP picked up significantly after oral administration for 30 days. The results showed that AP had positive influrence on the protection of β cells of pancreas island injured by STZ.

Table 4 Effect of AP on the insulin levels in serum of diabeticrats induced by STZ ($\bar{x} \pm s$)

Group	Doses (g/kg)	n	Serum insulin (MIU/L)	
			Before p.o	After p.o
Control		10	20.13± 6.08	21.2± 7.71
Model		10	6.38± 2.14	4.41± 2.24
XKW	2.5	10	6.48± 2.51	9.40± 2.40*
AP	0.25	10	5.99± 2.42	9.01± 2.31*
AP	0.125	10	6.38± 2.61	7.70± 3.42

Compared with model group* $P < 0.05$.

2.5 Histologic examination

As can be seen in Histologic examination, the pancreas is sublobe shape, and pancreatic island is round rope, dividing line clear, no inflammatory cell and fiber. There were 17 pancreatic islands and 36.2 island cells on average in each case in rats of control group. In the model group, number of pancreatic island decreased significantly, only 8 pancreatic islands on average in each case. Either its volume or its cell number decreased, showing little inflammatory cells and fiber tissue. The numbers of pancreatic island and its cells were significant increasing, and there were 15.7 pancreatic islands and 14.9 pancreatic island cells on average in each case, and no fibrosis in pancreatic island and only little cells were atrophy, but no inflammatory cells infiltration was found in AP groups. The results showed that AP had definite anti-oxidation, decreasing injuring of STZ on pancreatic island cells.

3 Discussion

The tender stem and leaves of Teng Cha have been used to treat with common cold and pyretic fever, pain-swelling of pharynx and larynx as well as jaundice hepatitis[4]. AP extracted from Teng Cha could resist constrictive action on rabbit thoracic aorta induced by epinephrine and high concetration K^+, thus expecting AP might be effective in treating with hypertension[5]. According to the previous studies, the flavonoid exhibits wide pharmacological activity on physiological systems of cardiovascular, respiratory and endocrine etc[6]. Thus, the results in our study showed that AP could lowered blood sugar levels in diabetic rats induced by STZ, increasing SOD activity and decreasing MDA content, levels of improving lipids, rising insulin levels in serum, and lightening the injuring of pancreatic island cells. Those suggests that AP has the effect of hypoglycemia, anti-oxidation, lipid-lowering, and protecting pancreatic island cells.

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而且最大误差都不超过0.2%，对有机酸及卤代烃等极性较强体系，误差稍大于其它类型体系。

4 结论

(1) 带阻尼的牛顿二阶学习方法，收敛快、精度高；(2) 本网络的工作区间 $[a_{min}, a_{max}]$ 为 [0.5, 0.7]，比较合适；(3) 本网络的学习平均误差很小，能满足绝大多数液体密度应用领域的要求。

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