Antidiabetic effect of GPAD from Coffee and its Mechanism

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Introduction

The diterpenoids in coffee are a critical component of coffee's activity, exhibiting a variety of properties, including antidiabetic activities.[1,2] Notably, diterpene glycosides—present in roasted *Arabica coffee* beans at 1-1.5 g/kg concentrations—functionas potential therapeutic targets for glucose metabolism regulation in diabetes management. 2-Glucopyranosyl atractyligenin (GPAD), a diterpenoid glycoside isolated with high yield from water extract of coffee, has attracted our attention. However, the antidiabetic effects of GPAD, particularly in db/db mice, remain largely unexplored. Preliminary in vitro studies demonstrated that GPAD significantly enhances glucose uptake in insulin-resistant HepG2 cells, outperforming other tested diterpenoids. This study aims to investigate the antidiabetic effects of GPAD and elucidate its underlying molecular mechanisms, providing a scientific basis for its potential therapeutic application in T2D management.

Matrerials and Methods

The antidiabetic effect of GPAD was tested in db/db mice, a well-established model of T2D. The results showed that GPAD significantly reduced fasting blood glucose levels, with the high-dose group demonstrating the most pronounced effect. Additionally, GPAD improved glucose tolerance, insulin sensitivity, and lipid profiles, while protecting against liver tissues damage induced by diabetes. The molecular mechanisms underlying these effects were further explored through RT-qPCR and immunohistochemistry.

Results & Discussion

GPAD treatment, particularly at high dose, significantly reduced fasting blood glucose by week 7, accompanied by marked improvements in glucose tolerance and insulin sensitivity. In addition to glycemic control, GPAD favorably modulated lipid profiles, lowering triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL) while increasing high-density lipoprotein (HDL). Molecular investigations revealed that GPAD activated the AMPK/PGC-1α/Sirt1 signaling pathway, evidenced by upregulating the mRNA levels of AMPKα1, phosphorylated AMPKα, Sirt1, and SOD1, restoring PGC-1α mRNA expression, and suppresing the mRNA levels of IL-6—suggesting a mechanistic basis for its metabolic regulatory effects. Importantly, cytotoxicity testing in HepG2 cells confirmed no significant toxicity at all tested concentrations, highlighting GPAD's safety and therapeutic potential for type 2 diabetes management. All the findings indicate that the antidiabetic effects of GPAD treatment may be achieved by enhancing the AMPK/PGC-1α/Sirt1 pathway, a well-established mechanism involved in regulating glucose and lipid metabolism, and cellular energy regulation.

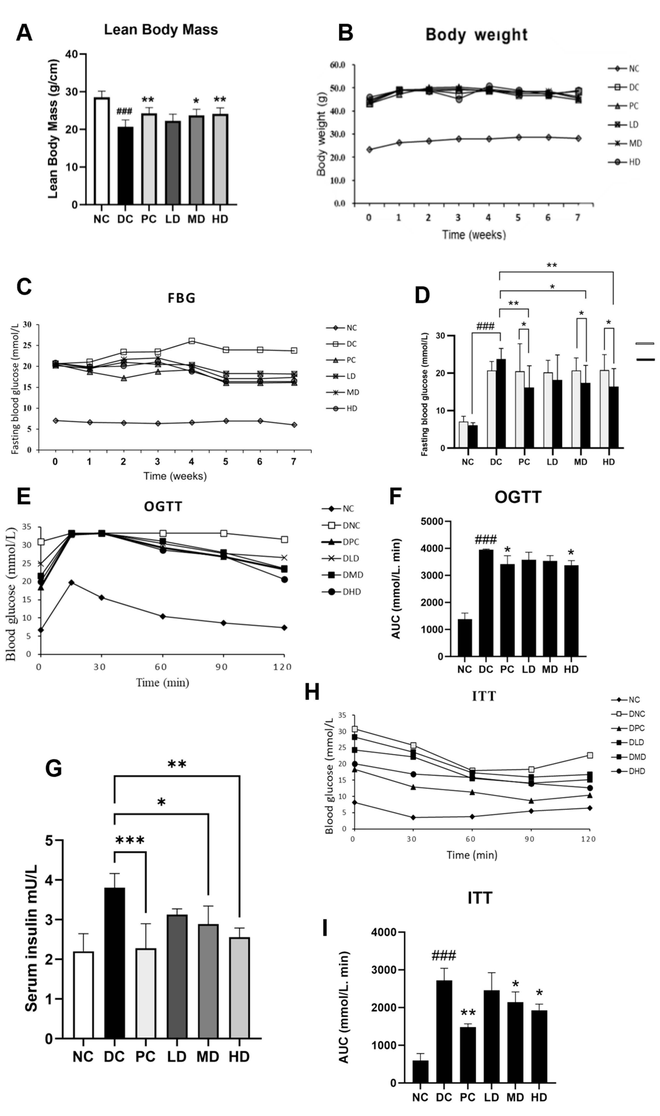

Fig. 1. Effect of GPAD on fasting blood glucose and glucose tolerance. (A) Lean body mass, (B) Body weight, (C,D) Fasting blood glucose during the period of treatment, (E, F) OGTT test and AUC of OGTT test, (G) Serum insilin level, (H,I) ITT test and AUC of OGTT test.

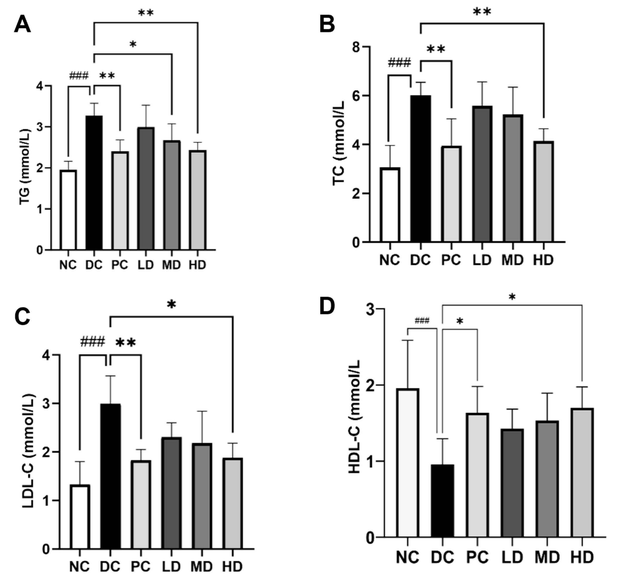

Fig. 2. Effects of GPAD on lipid parameters. (A) TG, (B) TC, (C) LDL, (D) HDL.

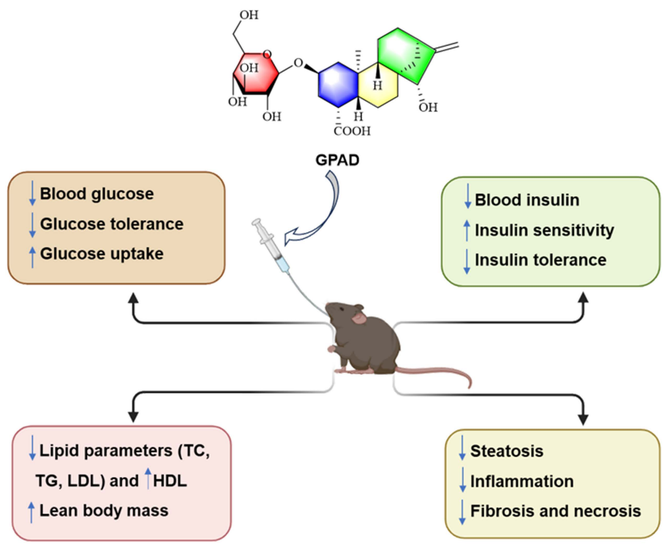

Fig. 4. The uderlying anti-diabetic mechainsm of GPAD.

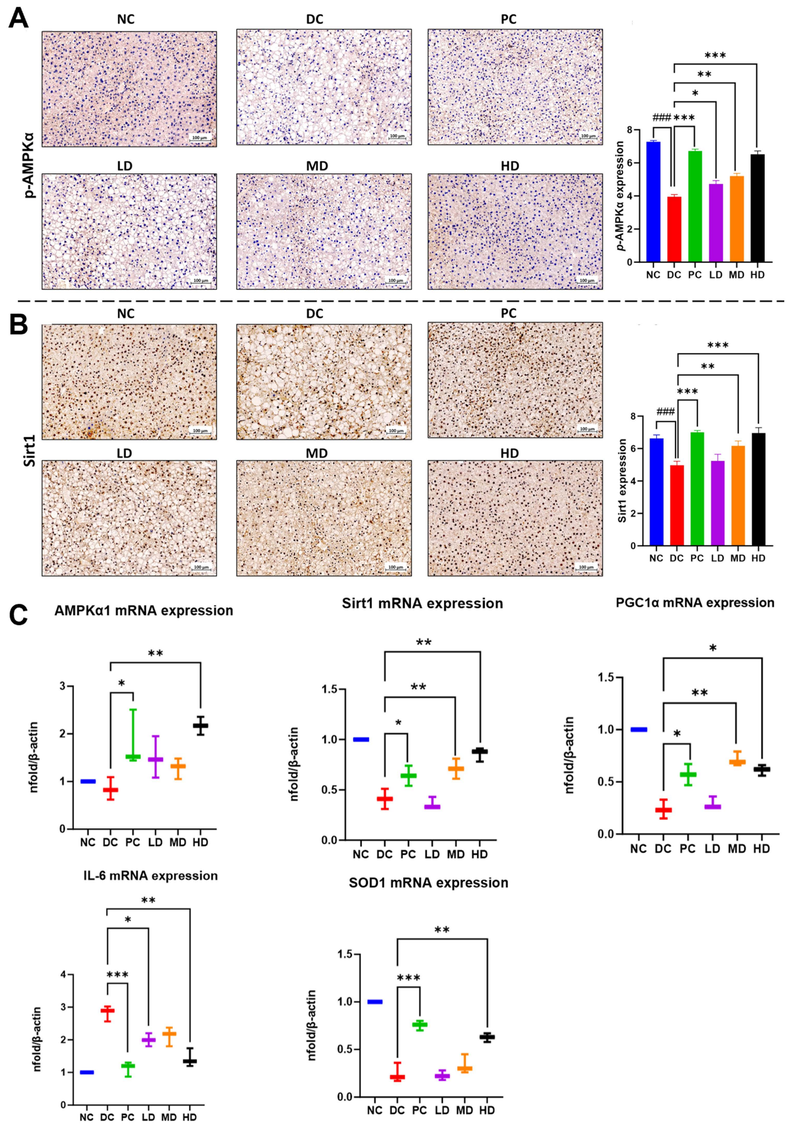

Fig. 3. Effect of GPAD on the expression level of some key protein and gene. (A,B) immunohistochemical staining and semiquantitative expression of p-AMPKα, Sirt1 in the liver tissues. (C) Relative mRNA expressions levels in the liver tissues.

Conclusion & Perspectives

These resaerch results showed that GPAD ameliorates insulin resistance and improves metabolic dysfunction by activating the AMPK pathway. GPAD is a promising candidate drug for controlling hyperglycemia.

References

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2. Hu, G. L.& Qiu, M. H. Food Chem., 2021, 345,128823.