INSULIN MIMICKING ACTIVITIES OF CYCLOARTANE TRITERPENOID IN 3T3-L1 CELLS

Poster ID: 1368

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INTRODUCTION

Type 2 diabetes is a metabolic disorder characterized by insulin resistance, insulin action and caused by multifactorial etiology, including environmental factors, particularly diet and genetic components. Recently, most research on diabetes has focus on adipocyte which is used as a model for testing of insulin sensitivity and novel antidiabetic drugs. Adipose tissue is the major fat depot of the body and an important endocrine organ which plays a major role in energy regulation and homeostasis. The differentiation and proliferation of pre-adipocyte (adipogenesis) is required to maintain the 'healthy' functions of adipose tissue[1]. It has been reported that peroxisome proliferator-activated receptor (*pparγ*) and glucose transport (*glut4*) performs a key role in lipid and glucose metabolism [2].

Pparγ activation in mature adipocytes regulates several genes involved in the insulin signaling cascade and glucose and lipid metabolism [3]. Since the incidence of diabetes and the resultant metabolic syndrome are rapidly increasing, this has opened the gap to search for an alternative therapy from natural products which can stimulate adipocyte differentiation, enhance blood glucose uptake, easily available and cost effective.

OBJECTIVES

To evaluate the *in vitro* activities of cycloartane triterpenoid on adipocyte differentiation, glucose uptake and related gene expression (*pparγ* and *glut4*) mechanism on adipocytes.

MATERIALS AND METHODOLOGY

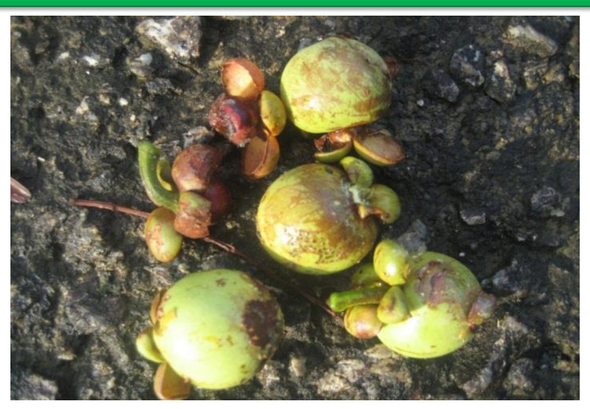


Fig. 1: The fruit of *Garcinia malaccensis*

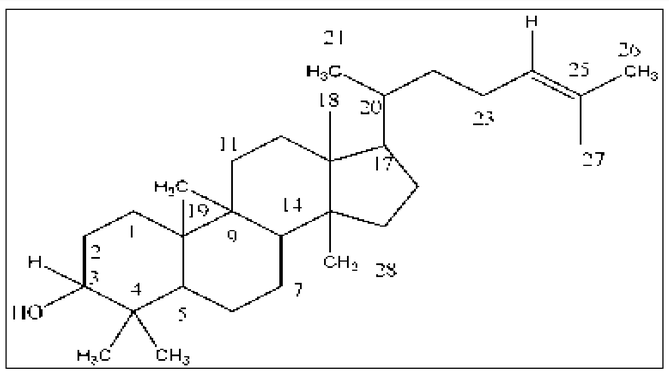


Fig. 2: Structure of Cycloart-24-en-3β-ol

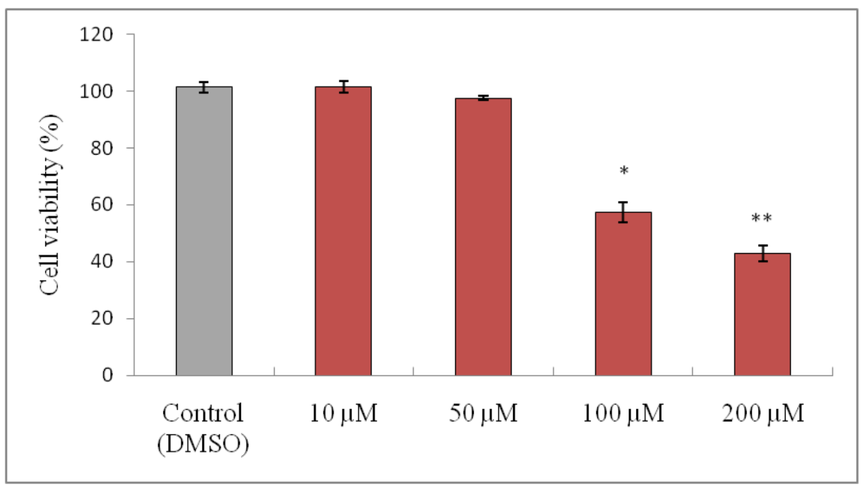


Fig. 3: Suitable dosage study (MTT)

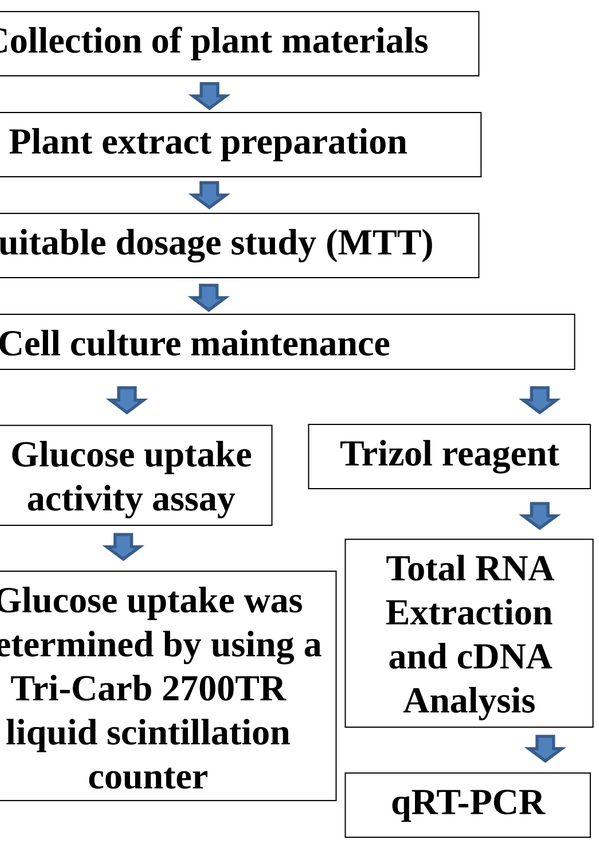
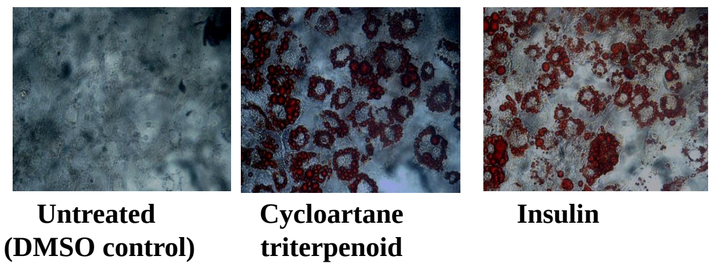


Fig. 4: Flowchart of the study

RESULTS AND DISCUSSION



Untreated (DMSO control) **Cycloartane triterpenoid** **Insulin**

Fig. 5: Oil Red O staining image

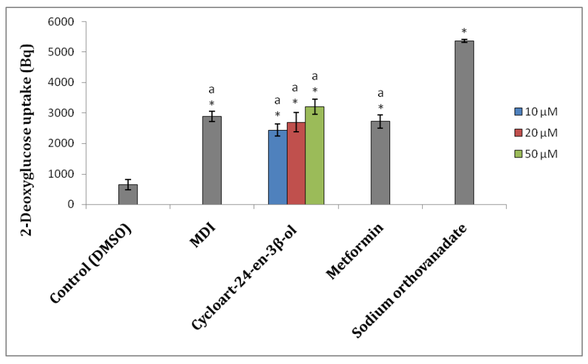


Fig. 7: 2-Deoxyglucose uptake analysis

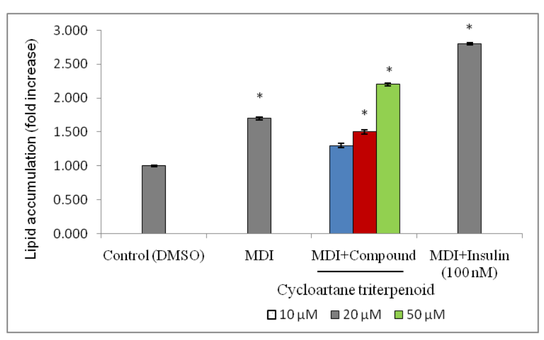


Fig. 6: Lipid accumulation (OD:520nm)

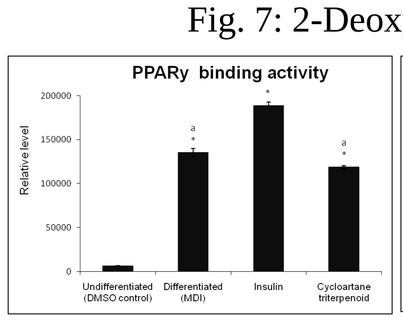


Fig. 8: *Pparγ* binding activity

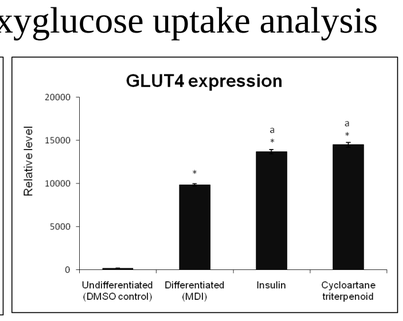


Fig. 9: *Glut4* expression

Before induction, 3T3-L1 preadipocyte were free from any lipid droplets. Cell treated with different concentration of the compound significantly enhance conversion of preadipocyte into mature adipocyte (adipocyte differentiation). The formation of lipid droplets and OD value which were significant with insulin (positive control) further supported this observation.

Figure 5: Effects of cycloartane triterpenoid on adipocyte differentiation. The Oil Red O stained adipocyte were photographed at magnification of 200x.

Figure 6: The intracellular fat accumulation increased by 1.9 fold relative to MDI-treated cells at concentration 50 µM. All values are presented as means ± SD of three independent experiments. *$p < 0.05$ vs. untreated group (DMSO control).

Figure 7: Glucose uptake assay. Adipocyte in 12-well plates were incubated for 60 minutes with cycloartane triterpenoid (50 µM) or with metformin (1mM) and sodium orthovanadate (5mM) as a positive control, or without treatment as a negative control. Levels of radioactivity in the cell lysates were determined using a liquid scintillation counter. Data are means ± SD, (n = 3). *$p < 0.01$ vs. untreated group (DMSO control).

Figure 8: Effect of cycloartane triterpenoid on *pparγ* binding activity. *Pparγ* expression was measured after 48 hours of treatment. *B-actin* was used as the control. Results are expressed as means ± SD.

Figure 9: *Glut4* expression. *Glut4* is the major insulin-dependent transporter responsible for the uptake of glucose from blood stream into muscle and fat.

CONCLUSION

It can be concluded that cycloartane triterpenoid follow almost similar pattern to that of insulin in adipocyte differentiation. In addition, it can effectively stimulate the peripheral glucose uptake at dose 50 µM. Through the quantitative RT-PCR evaluation, these findings suggest that cycloartane triterpenoid enhance adipocyte differentiation and glucose uptake by stimulation of PPARγ and GLUT4 expression.

FUTURE WORK / PROJECT POTENTIAL

The present study can provide a supportive information for a further study on the *in vivo* method using diabetic-induced animal and control group. Later, the compound can be commercialized as an alternative treatment for the management of diabetes and its related diseases.

REFERENCES

[1] Nawrocki, A. R., & Scherer, P. E. (2005). Keynote review: the adipocyte as a drug discovery target.
[2]Park, H. G., et al. (2011). Licochalcone E has an antidiabetic effect. Journal of Nutritional Biochemistry.
[3] Choi, S. S., et al. (2011). "Artepillin C; as a PPAR [gamma] ligand; enhances adipocyte differentiation and glucose uptake in 3T3-L1 cells." Biochemical pharmacology.

ACKNOWLEDGEMENT

This work was funded by Escience Fund (02-01-08-SF0110).