ISSN (Online) 2287-3406
Journal of Life Science **2022** Vol. 32. No. 2. 86~93 DOI : https://doi.org/10.5352/JLS.2022.32.2.86

Facilitation of Glucose Uptake by Lupeol through the Activation of the PI3K/AKT and AMPK Dependent Pathways in 3T3-L1 Adipocytes

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Received November 10, 2021 /Revised November 19, 2021 /Accepted November 21, 2021

Lupeol is a type of pentacyclic triterpene and has been reported to have pharmacological activities against various diseases; however, the effect of lupeol on glucose absorption has not been elucidated yet. This study aimed to investigate the effect of lupeol on glucose uptake in 3T3-L1 adipocytes. Lupeol significantly facilitated glucose uptake by translocating glucose transporter type 4 (GLUT4) to the plasma membrane of the 3T3-L1 adipocytes, which was related to activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and 5 'adenosine monophosphate-activated protein kinase (AMPK) pathways. In the PI3K/AKT pathway, lupeol stimulates the phosphorylation of insulin receptor substrate 1 (IRS-1), which activates PI3K. Its activation by lupeol promotes the phosphorylation of AKT, but not the atypical protein kinase C isoforms ζ and λ. Lupeol also promoted the phosphorylation of AMPK. The activation of AMPK increased the expressions of the plasma membrane GLUT4 and the intracellular glucose uptake. The increase in the glucose uptake by lupeol was suppressed by wortmannin (PI3K inhibitor) and compound C (AMPK inhibitor) in the 3T3-L1 adipocytes. The results indicate that lupeol can facilitate glucose uptake by increasing insulin sensitivity through the stimulation of the expression of plasma membrane glucose transporter type 4 via the PI3K/AKT and AMPK pathways in the 3T3-L1 adipocytes.

Key words : AMPK Pathway, glucose uptake, lupeol, PI3K pathway, 3T3-L1 adipocytes

Introduction

Hyperglycemia is a major symptom of type 2 diabetes and is caused by insulin secretory dysfunction and insulin resistance [2]. Insulin is a glucoregulatory hormone that keeps glucose homeostasis by inhibiting gluconeogenesis in the liver and promoting glucose uptake in muscle and adipose tissue [20]. Action of insulin on glucose uptake in muscle and adipose tissue is important for reducing hyperglycemia. In this action, translocation of the glucose transporter type 4 (GLUT4) to the plasma membrane can promote glucose uptake into cells [10]. The GLUT4 translocation to the plasma membrane begins with the combination of insulin and insulin receptor. It promotes tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1), which causes phosphoinositide 3-kinase (PI3K) expression. PI3K expression can act on two downstream targets. One is the serine / threonine kinase AKT and the other is the atypical protein kinase C isoforms ζ and λ (PKC ζ/ λ). Phosphorylation of AKT and PKC ζ/ λ stimulates GLUT4 translocation to the plasma membrane, which induces glucose uptake into the cells [19, 22].

Another key signaling mechanism that regulates glucose uptake is the 5 'AMP-activated protein kinase (AMPK). AMPK inhibits anabolic process and promotes catabolic processes to produce energy and decrease blood glucose level [7]. Activation of AMPK enhances intracellular glucose uptake by stimulating translocation of GLUT4 to the plasma membrane [9]. Thus, AMPK relates to glucose homeostasis in body and enhancement of insulin sensitivity by accelerating glucose uptake and energy expenditure [27]. These reports indicate that activation of the PI3K/AKT and AMPK pathways play a key role in glycemic control and could be therapeutic targets of type 2 diabetes.

Lupeol is a kind of pentacyclic triterpene, and its chemical formula is $C_{30}H_{50}O$ (lup-20(29)-en-3-ol) [4]. Lupeol has been reported to have pharmacologically active for diseases such as diabetes, cancer, heart diseases, inflammation, arthritis and hepatic toxicity [3, 23, 25]. However, the effect of lupeol on glucose uptake in adipocytes is not yet known. Therefore, this study investigated the lupeol effect on glucose uptake

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via PI3K/AKT and AMPK dependent pathways in 3T3-L1 adipocytes.

Materials and Methods

Materials

Lupeol (94%), was purchased from Sigma Aldrich (St. Louis, MO, USA). 3T3-L1 preadipocytes were purchased from Korean Cell Line Bank (KCLB, Seoul, Korea). Dulbecco modified Eagle medium (DMEM), fetal bovine serum (FBS), wortmannin, and compound C were purchased from Sigma (St. Louis, MO, USA). 2-Deoxy-2-[(7-nitro-2,1,3-benzoxadiazol-4-yl) amino]- d -glucose(2-NBDG) was purchased from Invitrogen (Carlsbad, CA, USA). Antibodies against IRS-1, PI3K, phospho-Akt, Akt, and GLUT4 were purchased from Abcam (Cambridge, UK). Antibodies against phospho-IRS-1 were purchased from Thermo Fisher Scientific (Rockford, IL, USA). All chemicals were of analytical grade and were used without any further purification.

Cell culture and differentiation

3T3-L1 preadipocytes (KCLB, Seoul, Korea) were cultured in high glucose (4.5 mM) Dulbecco's modified Eagle medium containing 10% fetal bovine serum at 37℃ temperature and 5% CO_2. Cultured 3T3-L1 preadipocytes were differentiated into adipocytes in the following way. 2 days after confluence, the culture medium was replaced with new Dulbecco's modified Eagle medium with 10% fetal calf serum, 0.5mM isobutyl methyl xanthine, 1 μM dexamethasone, and 10 μg/ml insulin. Afterwards, fresh 10% FBS DMEM with 10 μg/ml insulin was treated to the cells for an additional 24 hr, and maintained for 8 days [8].

Glucose uptake

Glucose uptake was conducted using the 2-[N-(7-nitobenz-2-oxa-1,3-diazol-4-yl) Amino]-2-deoxyglucose (2-NBDG) screening system, as described previously with partial modifications. Differentiated 3T3-L1 adipocytes of 1×10^4 density were seeded with several lupeol concentrations, WM and CC into each well of 96-well plates for 24 hr of incubation. The cells were left untreated or were stimulated with insulin (100 nM) for 20 min at 37℃ in Krebs-Ringer phosphate buffer solution (4.7 mM KCl, 128 mM NaCl, 1.25 mM $MgSO_4$, 1.25 mM $CaCl_2$, and 10 mM $NaPO_4$, pH 7.4). The addition of 2-NBDG (10 μM) to each well for 1 hr initiated glucose uptake for 1 hr. After the supernatant was removed, uptake of 2-NBDG was measured using a Multilabel Counter (Perkin Elmer, MA, USA) set at an excitation and emission wavelengths of 485 and 535 nm.

Western blotting

Cells were washed twice with ice-cold phosphate-buffered saline (PBS) and collected in RIPA buffer [Tris-HCl (50 mM), NaCl (150 mM), EDTA (1 mM), Triton X-100 (1%), sodium deoxycholate (1%), sodium dodecyl sulfate (0.1%), phenylmethylsulfonyl fluoride (1 mM), aprotinin (10 μg/ml), leupeptin (10 μg/ml), sodium orthovanadate (0.1 mM); pH 7.4] for whole protein extraction from 3T3-L1 adipocytes. After sonication and centrifugation at 13,000 rpm for 15 min at 4℃, a bicinchoninic acid (BCA) Protein Assay Kit was used to determine the protein content in the resulting supernatant. The lysate containing 20 μg protein was subjected to 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Isolated proteins were transferred electrophoretically to a pure nitrocellulose membrane, blocked with a 5% skimmed milk solution for 1 hr, and then incubated with primary antibodies [IRS-1, PI3K, phospho-AktSer473, Akt, AMPK, GLUT4 (Abcam, Cambridge, UK), phospho-AMPKThr172, ACC (Cell Signaling Technology, Beverly, MA, USA), phospho-IRS-1Tyr612 (Thermo Fisher Scientific, Rockford, IL, USA), phospho-ACCSer79 (EMD Millipore, Billerica, MA, USA)] overnight at 4℃. After rinsing, the blots were cultured with horseradish peroxidase-conjugated goat anti-rabbit or goat anti-mouse IgG (secondary antibody) for 1 hr at room temperature. The antigen-antibody complexes were visualized using enhanced chemiluminescence western blotting detection reagents and detected by a Luminoimage Analyzer LAS-1000 plus (Fujifilm, Tokyo, Japan). The density of the bands was determined using an image analyzer (Multi Gauge V3.1, Fujifilm, Valhalla, NY, USA) and normalized to the β-actin chemiluminescence signal for relative total and nuclear protein quantification.

Isolation of plasma membranes from 3T3-L1 adipocytes

The 3T3-L1 cells were homogenized using sonication for 5 min at 3 kHz/130 W (UCD-130TM, Cosmo Bio Co., Tokyo, Japan) in ice-cold HES buffer [HEPES (0.02 M), sucrose (0.25 M), and EGTA (0.002 M); pH 7.4] and centrifuged at 700 × g for 7 min for removing non-homogenized cellular debris and nuclei from the homogenate. To eliminate mitochondria the gathered supernatant was further centrifuged at 760×

g for 10 min. After re-centrifugation at 35,000× g for 1 hr, the obtained pellet was used as the plasma membrane fraction. And the remaining supernatant was used as a cytosolic fraction. To detect GLUT4 protein, these membrane and cytosolic fractions were exposed to western blotting. The concentration of proteins in the cytosolic fraction and membrane pellet was quantified with a BCA protein assay kit.

Statistical analyses

Data were expressed as the mean ± standard error of three experiments. The statistical analysis was performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA). The differences were evaluated by the one-way ANOVA test, followed by the post hoc Duncan's multiple range tests.

Results

Effect of lupeol on glucose uptake

This study examined a 2-deoxyglucose uptake to find out the effect of lupeol on glucose uptake in 3T3-L1 adipocytes. Treatment with lupeol enhanced uptake of glucose in a concentration dependent manner (Fig. 1). At 5, 10, 15 and 20 μM concentration of lupeol, glucose uptake was remarkably increased 1.68-, 2.00-, 2.28- and 2.49- fold in comparison with untreated control cells, respectively. These data suggest that lupeol was effective in enhancing uptake of glucose in 3T3-L1 adipocytes.

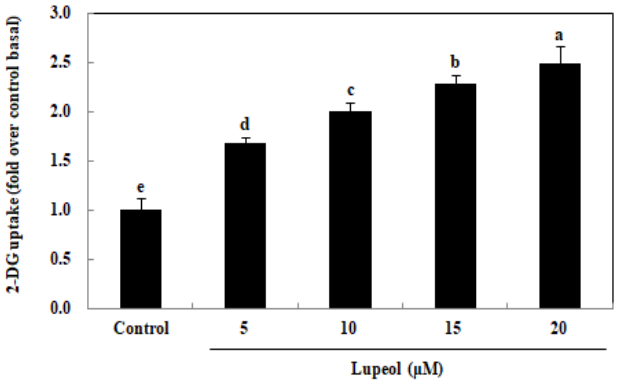

Fig. 1. Effect of lupeol on glucose uptake in 3T3-L1 adipocytes. Lupeol of 5-20 μM were treated in 3T3-L1 adipocytes for 24 hr prior to the 2-deoxyglucose uptake assay. Each value is shown as the mean ± standard deviation (n=3). [a-e]Values composed of different alphabets indicate significant differences (p<0.05) by Duncan's multiple range test. 2-DG, 2-deoxyglucose.

Effect of lupeol on the activation of PI3K/AKT pathway

To investigate the mechanism that lupeol improves glucose uptake, the activation of IRS-1, PI3K, PKC ζ/λ or AKT was examined in insulin signaling pathway. Lupeol significantly enhanced IRS-1 phosphorylation and PI3K activation in 3T3-L1 adipocytes (Fig. 2). Treatment of 10 and 20 μM lupeol upregulated IRS-1 phosphorylation to 119.61% and 151.63% of the control values, respectively. At the same concentration, the expression of PI3K was significantly increased to 143.75% and 192.50% of the control values, respectively. Also, the phosphorylation of AKT was increased to 138.89% and 188.89% of the control values by treatment of 10 and 20 μM lupeol, respectively. But the phosphorylation of PKC ζ/λ was not affected by lupeol treatment (Fig. 3). These data indicated that lupeol promoted the phosphorylation of IRS-1 and the activation of PI3K and AKT, but did not promote phosphorylation of PKC ζ/λ in the insulin signaling pathway.

Effect of lupeol on AMPK activation

To examine the mechanism that lupeol improves uptake of glucose, we investigated the phosphorylation of AMPK. Phosphorylation of ACC was also examined to confirm the activation of AMPK. AMPK activation phosphorylates ACC and inhibits its activity [8]. Lupeol showed significant increasing effect on phosphorylation of AMPK (Fig. 4). The phosphorylation of AMPK was significantly increased to 137.54% and 186.32% of the control values by treatment of 10 and 20 μM lupeol, respectively. At the same concentration, the phosphorylation of ACC was also increased to 101.67% and 155.83% of the control value, respectively. These data suggest that lupeol may enhance glucose uptake into adipocytes by promoting the phosphorylation of AMPK.

Effect of lupeol on PM-GLUT4 expression

To find out the role of GLUT4 on glucose uptake enhanced by lupeol, expression of plasma membrane GLUT4 was examined in 3T3-L1 adipocytes. Lupeol treatment significantly increased expression of plasma membrane GLUT4 in 3T3-L1 adipocytes (Fig. 5). 20 μM lupeol increased plasma membrane GLUT4 expression to 155.29% of control value. However, treatment of lupeol with wortmannin, PI3K inhibitor, or Compound C, AMPK inhibitor, significantly decreased plasma membrane GLUT4 expression in 3T3-L1 adipocytes. When 20 μM lupeol plus 20 μM WM was treated

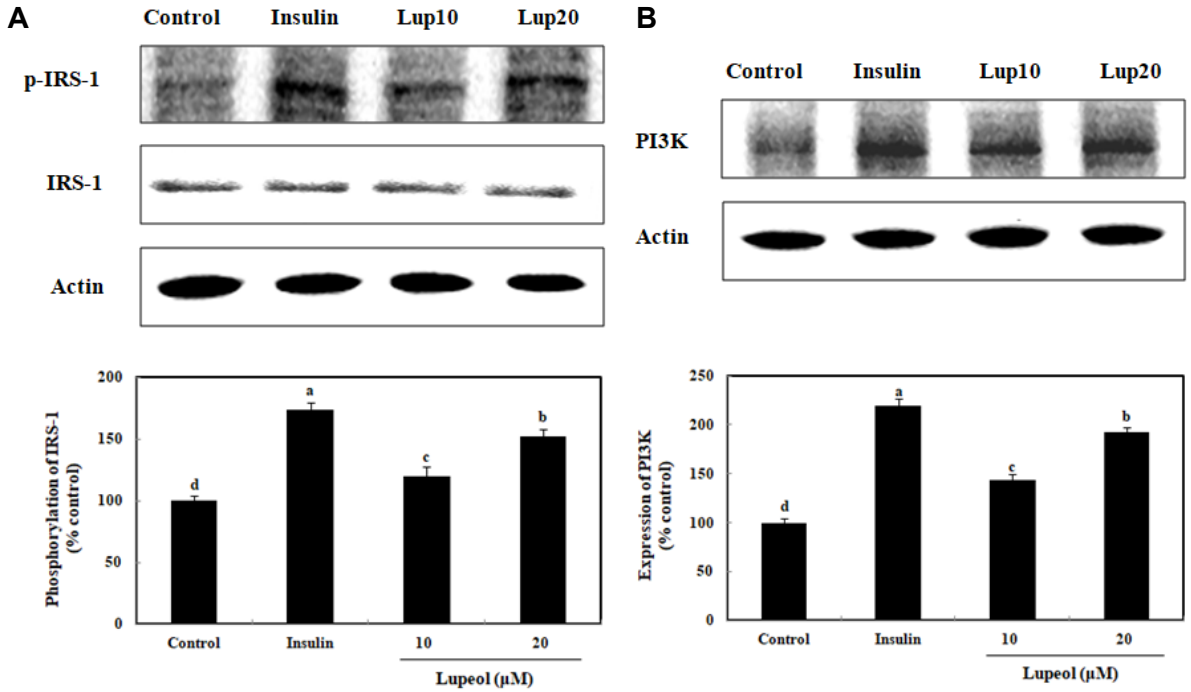

Fig. 2. Effects of lupeol on the expression of IRS-1 and PI3K in 3T3-L1 adipocytes. Lupeol of 10, 20 μM or insulin of 100 nM were treated in 3T3-L1 adipocytes for 24 hr, after that, lysed cells were performed to Western blotting. (A) Phosphorylation value of insulin receptor substrate-1, (B) Expression value of phosphoinositide 3-kinase. Each value is shown as the mean ± standard deviation (n=3). [a-d]Values composed of different alphabets indicate significant differences (p<0.05) by Duncan's multiple range test.

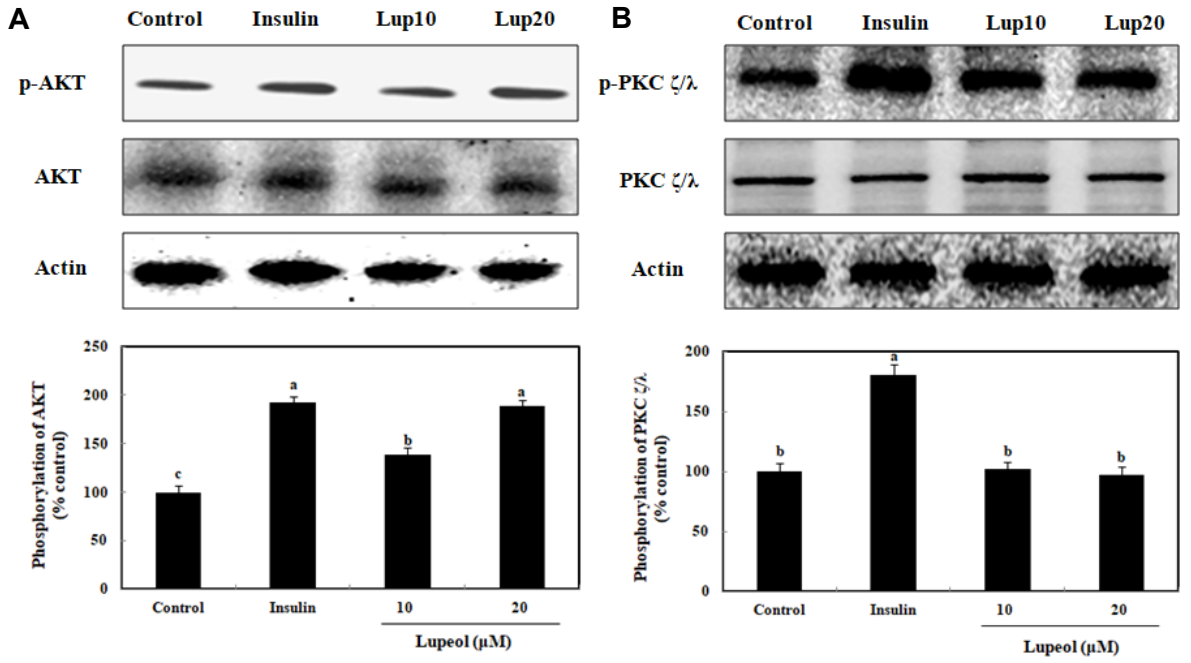

Fig. 3. Effects of lupeol on the expression of AKT and PKC ζ/λ in 3T3-L1 adipocytes. Lupeol of 10, 20 μM or insulin of 100 nM were treated in 3T3-L1 adipocytes for 24 hr, after that, lysed cells were performed to Western blot analysis. (A) Phosphorylation value of AKT, (B) Phosphorylation value of protein kinase C ζ/ λ. Each value is shown as the mean ± standard deviation (n=3). [a-c]Values composed of different alphabets indicate significant differences (p<0.05) by Duncan's multiple range test.

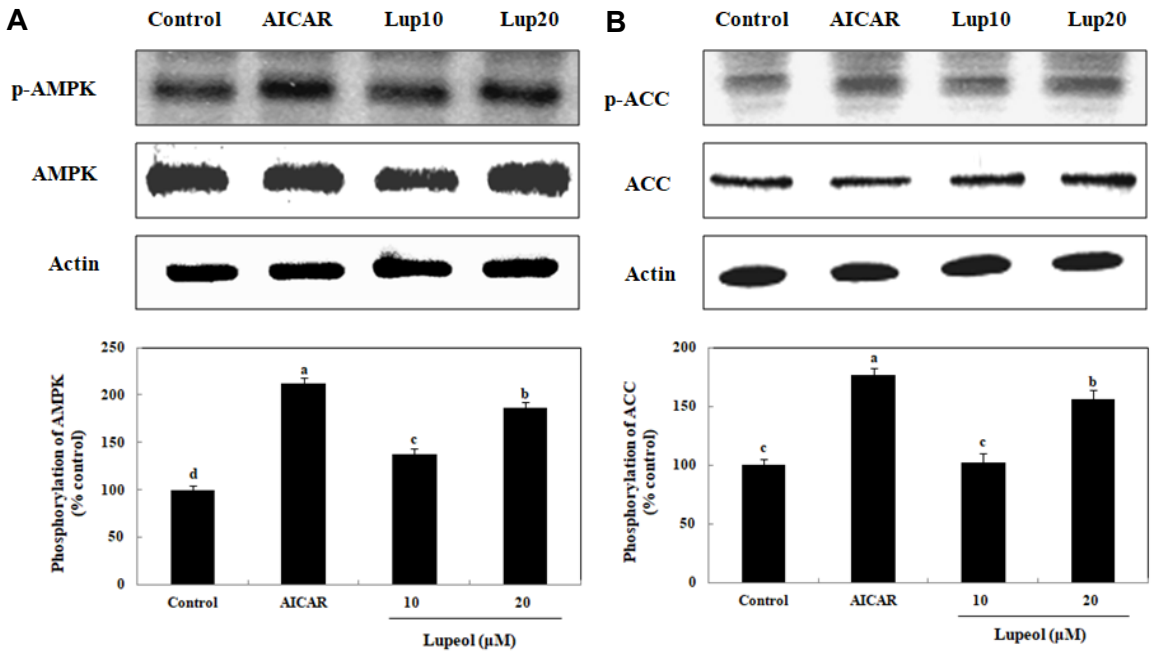

Fig. 4. Effects of lupeol on the expression of AMPK and ACC in 3T3-L1 adipocytes. Lupeol of 10, 20 μM or AICAR of 0.5 mM were treated in 3T3-L1 adipocytes for 24 hr, after that, lysed cells were performed to Western blot analysis. (A) Phosphorylation value of 5 'AMP-activated protein kinase, (B) Phosphorylation value of acetyl-CoA carboxylase. Each value is shown as the mean ± standard deviation (n=3). [a-d]Values composed of different alphabets indicate significant differences (p<0.05) by Duncan's multiple range test.

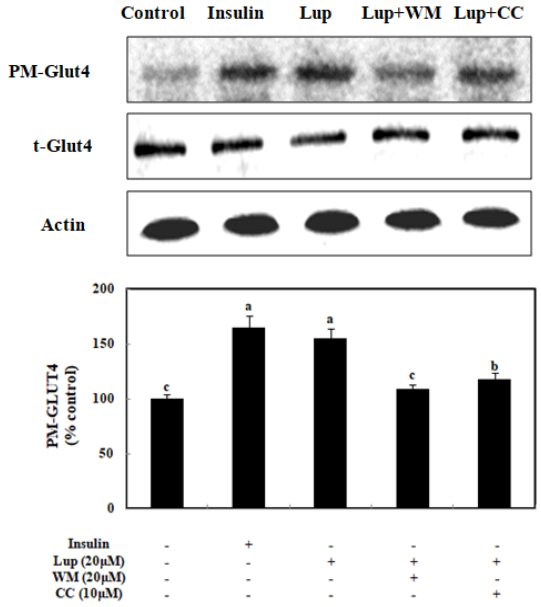

Fig. 5. Effect of lupeol on PM-GLUT4 expression in 3T3-L1 adipocytes. 20 μM lupeol and its combination with 20 μM WM or 10 μM CC and 100 nM insulin were treated in 3T3-L1 adipocytes for 24 hr, after that, lysed cells were performed to Western blot analysis. Each value is shown as the mean ± standard deviation (n=3). [a-c]Values composed of different alphabets indicate significant differences (p<0.05) by Duncan's multiple range test. WM, wortmannin; CC, compound C.

to cells, the expression of plasma membrane GLUT4 was significantly decreased to 108.82% from the 155.29% value treated with lupeol alone. Treatment with 20 μM lupeol plus 10 μM CC also decreased expression of plasma membrane GLUT4 to 117.65% from 155.29% value treated with lupeol alone. These data indicated that lupeol stimulated the translocation of GLUT4 to the plasma membrane via PI3K/AKT and AMPK pathways.

Effect of lupeol added with wortmannin (WM) or compound C (CC) on glucose uptake in 3T3-L1 adipocytes

A 2-deoxyglucose uptake assay was implemented to indicate the effect of lupeol added with WM or CC in 3T3-L1 adipocytes. Glucose uptake was significantly enhanced by the treatment of lupeol in 3T3-L1 adipocytes (Fig. 6). The cells treated with 20 μM lupeol increased glucose uptake by 2.49-fold compared to untreated control cells. However, when lupeol (20 μM) was added with WM (20 μM), glucose uptake decreased to 1.33-fold. Similarly, the treatment combined with lupeol (20 μM) and CC (10 μM) also significantly decreased glucose uptake to 1.55-fold. These results suggest that lupeol may enhance glucose uptake through PI3K/AKT and AMPK pathways in 3T3-L1 adipocytes.

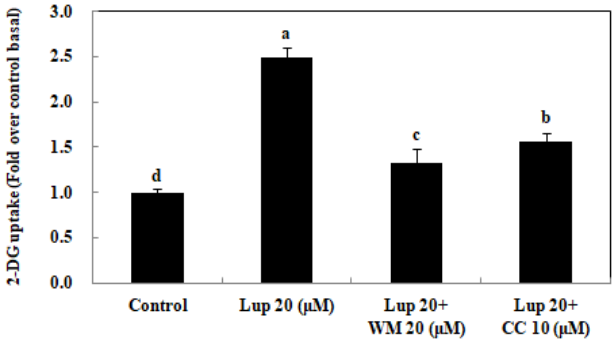

Fig. 6. Effect of lupeol combined with wortmannin of compound C on glucose uptake in 3T3-L1 adipocytes. 20 μM lupeol, its combination with 20 μM WM or 10 μM CC were treated in 3T3-L1 adipocytes, after that, 2-deoxyglucose uptake assay was conducted. Each value is shown as the mean ± standard deviation (n=3). [a-d]Values composed of different alphabets indicate significant differences (p<0.05) by Duncan's multiple range test. WM, wortmannin; CC, compound C.

Discussion

As shown in various studies, natural compounds are effective in preventing and treating disease, but without side effects [5]. Among them, triterpenoid compounds are known to have several beneficial effects including antidiabetic activity [18]. Lupeol is a type of pentacyclic triterpene, and has been proven to have pharmacological activities and therapeutic effects [16]. However, the effects of lupeol on glucose uptake and mechanisms have not been elucidated yet. Therefore, this study was conducted to investigate the effect of lupeol on glucose uptake and clarify the cellular mechanisms about this effect in 3T3-L1 adipocytes. The pathogenesis of type 2 diabetes reduced glucose uptake into cells due to impaired insulin action [6]. Insulin is an important hormone in maintaining blood glucose homeostasis and stimulates glucose uptake by activating insulin signaling pathway in muscle and adipose tissue [30].

Lupeol significantly increased glucose uptake in 3T3-L1 adipocytes. This means that lupeol can enhance glucose uptake into the cells to reduce hyperglycemia. Enhancing glucose uptake is important to reduce hyperglycemia in adipocytes [21]. Glucose uptake is facilitated by plasma membrane GLUT4 in adipocytes. Translocation of GLUT4 to the plasma membrane is stimulated through activation of two pathways, the PI3K/AKT and AMPK pathways. Activation of these two pathways stimulates GLUT4 translocation to the plasma membrane and transports glucose into the cells [9, 19, 22, 27].

To find out the action mechanism on the glucose uptake of lupeol, we investigated PI3K pathway. In this pathway, insulin binds to the insulin receptor and stimulates phosphorylation of IRS-1. PI3K activation induced by phosphorylated IRS-1 activates Akt-mediated pathway or atypical PKC-mediated pathway. Akt or PKC ζ /λ activation causes translocation of GLUT4 to the plasma membrane and finally intracellular glucose uptake is enhanced [19, 22]. This study confirmed that lupeol significantly increased phosphorylation of IRS-1 and activation of PI3K in 3T3-L1 adipocytes. Moreover, lupeol increased phosphorylation of AKT through PI3K activation in 3T3-L1 adipocytes, but it was not effective in phosphorylation of PKC ζ /λ. Phosphorylation of AKT translocated GLUT4 to plasma membrane and promoted intracellular glucose uptake. The data suggest that lupeol might improve glucose uptake through the PI3K/AKT pathway in adipocytes.

Lupeol belongs to the pentacyclic triterpene, a bioactive compound present in some medicinal plants [23]. At the 3-beta position of lupeol, hydrogen is substituted with a hydroxyl group [4]. One study has revealed reported that jujube methanol extract had a glucose uptake-promoting effect with betulonic, oleanonic and ursolic acids identified as the active compounds [15]. These active compounds are pentacyclic triterpenoids those are substituted by a beta-hydroxy group at position 3, such as lupeol. Furthermore, several studies reported that triterpenoids possess hypoglycemic effects by regulating insulin sensitivity in various cell models. Corosolic acid stimulates glucose uptake via promoting insulin receptor phosphorylation [24]. Also, ursolic acid enhanced glucose uptake by activating PI3K/AKT signaling pathway in 3T3-L1 adipocytes [11]. These results suggest that the presence of 3-hydroxyl groups in pentacyclic triterpenoids is important for the glucose uptake activity. Therefore, lupeol may help in the treatment of diabetes by activating insulin signaling pathway to improve glucose uptake.

The activation of the AMPK is considered to be one of the key mechanisms on the glucose uptake and is attracting attention as a pharmacological target for the treatment of insulin resistance [28]. The phosphorylation of AMPK increases glucose uptake by translocating GLUT4 to the plasma membrane via insulin independent AMPK pathway in adipocytes [13]. Drugs such as 5-Aminoimidazole-4-carboxamide-1-β-4-ribofuranoside (AICAR), known as the AMPK

activator, stimulate activation of AMPK pathway [14]. To find out the effect of lupeol on activation of the AMPK pathway, the level of AMPK phosphorylation were examined in lupeol-treated 3T3-L1 adipocytes. Lupeol significantly increased phosphorylation of AMPK. It was also confirmed by the increase in phosphorylation of ACC. The result suggests that lupeol may also stimulate glucose uptake via the insulin-independent AMPK pathway.

AMPK consists of a catalytic α subunit and two regulatory subunits, β and γ. In this structure, α domain and β domain linked by small molecule activator include phosphorylated serine that is critical for the activation of AMPK [12]. Plectranthoic acid is one of the pentacyclic triterpenoids with carboxylate and hydroxyl group. The carboxylate of plectranthoic acid is hydrogen bonding to the phosphate of the serine in the β domain while hydroxyl of plectranthoic acid accepts a proton in the α domain, resulting in AMPK activation [1]. Also, betulinic acid, another pentacyclic triterpene, has been identified as an AMPK activator [26]. Therefore, lupeol may activate AMPK with similar structural basis.

Insulin resistance, a hallmark of type 2 diabetes, is a decrease in glucose transport and metabolism in muscle and fat cells. GLUT4 transfers from intracellular storage to the plasma membrane, mediating insulin-stimulated glucose uptake [17]. When postprandial blood glucose levels rise, circulating insulin increases and the intracellular insulin signaling cascades is activated, ultimately translocating GLUT4 to the plasma membrane [29]. The PM-GLUT4 expression can be influenced by the activation of PI3K/AKT and AMPK pathways [31]. Treatment of lupeol significantly enhanced GLUT4 translocation to the plasma membrane in 3T3-L1 adipocytes. We found that treatment of wortmannin and compound C, which are PI3K and AMPK inhibitor, respectively, inhibited the expression of PM-GLUT4 and decreased glucose uptake by lupeol in 3T3-L1 adipocytes. These data showed lupeol may increase the activation of the PI3K/AKT and AMPK dependent pathways and stimulate GLUT4 translocation to plasma membrane, thereby enhancing glucose uptake.

In conclusion, lupeol improves glucose uptake by stimulating the PI3K/AKT and AMPK pathways in 3T3-L1 adipocytes. Activation of PI3K and AMPK by lupeol was confirmed by PI3K inhibitor or AMPK inhibitor, and these inhibitors inhibited the expression of PM-GLUT4 by lupeol. It indicated that lupeol enhanced glucose uptake by up-regulating insulin sensitivity in 3T3-L1 adipocytes.

The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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초록 : 3T3-L1 지방세포에서 PI3K/AKT 및 AMPK 경로의 활성화를 통한 루페올의 포도당 흡수촉진 효과

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Lupeol은 pentacyclic triterpene의 일종으로 다양한 질병에 약리 효과가 있는 것으로 보고되어 있으나, lupeol이 포도당 흡수에 미치는 영향은 아직 보고된 바 없다. 본 연구에서 3T3-L1 지방세포에서 포도당 흡수에 대한 lupeol의 효과를 조사하였다. 그 결과, Lupeol은 3T3-L1 지방세포에서 GLUT4를 원형질막으로 이동시켜 포도당 흡수를 촉진하였으며, 이는 PI3K/AKT 및 AMPK 경로의 활성화와 관련되어 있었다. PI3K/AKT 경로에서 lupeol은 PI3K를 활성화시키는 insulin receptor substrate 1의 인산화와 AKT의 인산화를 촉진하지만 비정형 단백질 키나아제 C isoforms ζ 및 λ의 인산화는 촉진하지 않았다. 반면, lupeol은 5 ′AMP-activated protein kinase의 인산화를 촉진하였고, Lupeol의 의한 AMPK의 활성화는 원형질막-GLUT4의 발현과 세포내 포도당 흡수를 증가시키는 것으로 확인되었다. 3T3-L1 지방세포에서 lupeol에 의한 포도당 흡수 효과는 PI3K 억제제인 wortmannin 및 AMPK 억제제인 Compound C에 의해 억제됨을 통해 확인하였다. 본 연구 결과는 lupeol이 3T3-L1 지방세포에서 PI3K/AKT 및 AMPK 경로를 통해 원형질막 GLUT4의 발현을 자극함으로써 인슐린 감수성을 증가시켜 포도당 흡수를 촉진할 수 있음을 제시하고 있다.