Polydatin Improves Glucose and Lipid Metabolisms in Insulin-Resistant HepG2 Cells through the AMPK Pathway

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Type 2 diabetes mellitus (T2DM) occurs when the body becomes immune to insulin and impacts 90 to 95% of diabetic patients. Crucial to T2DM are changing levels of hyperglycemia coupled with dyslipidemia. Dyslipidemia may advance insulin resistance.1 Glucose and lipid digestion issues can occur by changing diabetic vascular entanglements. Stable glucose-lowering and lipid-lowering medicines can effectively reduce the movement of such inconveniences. Accordingly, it is essential to examine drugs with both hypoglycemic and hypolipidemic impacts for diabetes treatments.

AMP-activated protein kinase (AMPK) can be characterized as phylogenetically rationed intracellular vitality sensors that can control glucose and lipid homeostasis.3) Regulating insulin resistance.1,2) Glucose and lipid digestion issues can occur by changing diabetic vascular entanglements. Stable glucose-lowering and lipid-lowering medicines can effectively reduce the movement of such inconveniences. Accordingly, it is essential to examine drugs with both hypoglycemic and hypolipidemic impacts for diabetes treatments.

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AMPK action is complex due to allosteric actuation by AMP.5) Metformin5) and thiazolidinedione (TZDs) are viewed as fundamental hypoglycemic medications.6) Both of which are considered rate-restricting proteins involved in combining unsaturated fats by catalyzing ATP-subordinate carboxylation of acetyl-CoA to create malonyl-CoA, which is then changed to long-chain unsaturated fats by unsaturated fat amalgamation. Hence, AMPK can hinder the movement of ACC by phosphorylation and advance the usage and oxidation of unsaturated fats. Besides, AMPK can mediate Ser372 phosphorylation, inhibit sterol regulatory element-binding protein (SREBP)-1c cleavage and nuclear translocation, and inhibit SREBP-1c target quality expression in high glucose hepatocytes, thereby prompting decreased lipogenesis and lipid aggregation.

Several examinations have indicated that resveratrol can lessen hyperglycemia7) and damage caused to pancreas islet B cells8,9) and insulin resistance10,11) in diabetic patients through different components. Notwithstanding, the convergence of polydatin (3,4′,5-trihydroxystibene-3-β-mono-D-glucoside) is seven times that of resveratrol exhibited in red wine and Polygonum cuspidatum Sieb. and Zucc.12) Previous studies have reported the effects of polydatin on glucose and lipid metabolism regulation through activation of the protein kinase B (Akt) signaling pathway. Additionally, the effect of polydatin on increasing Akt phosphorylation is independent of prompt-
ing insulin secretion, and is instead dependent on increased insulin receptor substrate (IRS) phosphorylation.\textsuperscript{13} Several results\textsuperscript{14} have indicated that both glycosylated resveratrol and polydatin (Fig. 1) can hold natural exercises and protection from enzymatic oxidation, especially in plant cells. Other results\textsuperscript{15} have demonstrated that polydatin is the primary substance in serum after intragastrical organization with polydatin or resveratrol; hence, the common change between them can maintain a balanced state. Accordingly, polydatin can be preferably assimilated over resveratrol in v\textit{ivo}, and offers insight into the use of resveratrol for malady cures and counteractive action. In any case, both have the same metabolites\textsuperscript{16–18} and along these lines bioactive instruments. In this manner, research into resveratrol may likewise profit the information and comprehension of polydatin. Also, polydatin has been shown to affect irritation and oxidation by intervening receptive oxygen species age and mitochondrial function.\textsuperscript{19,20} To date, the lipid control of polydatin has attracted considerable consideration.\textsuperscript{21,22} Past examinations involving diabetic rats have demonstrated polydatin to have hypoglycemic effects.\textsuperscript{23} Resveratrol can initiate AMPK in several ways. For example, 3'-hydroxy gathering assumes a basic part against metabolic disorders such as AMPK activation.\textsuperscript{24} Therefore, it is concluded that polydatin can initiate the AMPK pathway to direct glucose and lipid digestion in trial diabetic models.

In the present investigation, we theorize that polydatin has comparable impacts for enhancing hyperglycemia and insulin protection similar to resveratrol, and the hidden component of which may identify with the AMPK pathway.

**MATERIALS AND METHODS**

**Cell Culture** Human hepatoma HepG2 cells were obtained from American Type Culture Collection (ATCC, Manassa, VA, U.S.A.). The cells were refined at 37°C in high glucose (25 mM) Dulbecco’s modified Eagle’s medium (DMEM, Gibco, Invitrogen Corporation, U.S.A.) with 10% (v/v) fetal bovine serum (Gibco) and 1% L-glutamic acid (Glu). HepG2 cells were dispersed by 0.25% trypsin-ethylenediaminetetraacetic acid (EDTA) (Gibco) and sub-refined in a proportion of 1:3. At the sub-juncture, HepG2 cells were serum-denied for 24 h and isolated into various gatherings for various medicines. HepG2 cells were secured with Collagen I (2–5 µg/cm², Invitrogen).

Cells were preincubated with or without polydatin (Chuangwei, Beijing, China) in 10, 20, and 40 µM measurements for 2 h, and animated with or without 100 nM of insulin (Beyotime, Haimen, Jiangsu, China) for 24 h. The cells were gathered following 10 min of insulin (100 nM) incitement for various estimations.

**Western Blot Analysis** Western blot examination was performed as described.\textsuperscript{25} Cells were lysed in radio immunoprecipitation assay (RIPA) lysis cushion (pH 8.0, 50 mM Tris, 150 mM NaCl, 0.02% sodium azide, 0.1% sodium dodecyl sulfate (SDS), 1% NP-40, 0.5% sodium deoxycholate, and 1 mM EDTA) supplemented with phenylmethylsulfonyl fluoride (1 mM; Sigma, U.S.A.) protease, and phosphatase inhibitor mixed drink (100×; Thermo, U.S.A.). For the extraction of nuclear and cytoplasmic proteins of HepG2, a commercialized assay kit (Active Motif, CA, U.S.A.) was used according to manufacturer protocols. Equal amounts of protein samples were separated by 8% (v/v) SDS-polyacrylamide gel electrophoresis (PAGE) and transported onto a polyvinylidene difluoride (PVDF) or a nitrocellulose (NC) film. In the wake of washing, the layers were brooded overnight at 4°C with one of these primary antibodies: rabbit polyclonal antibodies against p-AMPK (Thr172; Cell Signaling Technology, Cat. No. 2535, U.S.A.), P-ACC (Ser79; Cell Signaling Technology, Cat. No. 11818), AMPK (Cell Signaling Technology, Cat. No. 5831), ACC (Cell Signaling Technology, Cat. No. 3676), P-Akt (ser473, Cell Signaling Technology; Cat. No. 4060), P-glycogen synthase kinase (GSK)-3β (ser9; Cell Signaling Technology, Cat. No. 5558), GSK-3β (1:1000; Cell Signaling Technology, Cat. No. 9315), and SREBP-1c (1:300; Santa Cruz Biotechnology, Cat. No. sc-17755, U.S.A.); rabbit monoclonal immune response against low-density lipoprotein receptor (LDLR) (1:1000; Proteintech, Cat. No. 10785-1-AP, U.S.A.) and Akt (pan; 1:1000; Cell Signaling Technology, Cat. No. 4691); mouse monoclonal immunizer against low-density lipoprotein receptor (LDLR) (1:1000; Proteintech, Cat. No. 10785-1-AP, U.S.A.) and Akt (pan; 1:1000; Cell Signaling Technology, Cat. No. 4691); mouse monoclonal immunizer against Tubulin (1:10000; Sigma), Actin (1:1000; Beyotime) and Histone 1.4 (1:10000; Sigma). After further washing, the films were hatched for 1 h by comparing horseradish peroxidase-conjugated optional antibodies (hostile to rabbit immunoglobulin G (IgG) or hostile to mouse IgG, 1:10000; Promega, U.S.A.). Immunoreactive groups were pictured by an upgraded chemiluminescence substrate (Thermo Fisher Scientific, Rockford, IL, U.S.A.) with a GE ImageQuant LAS 4000 mini (GE Healthcare, Waukesha, WI, U.S.A.). The intensity of the protein groups was quantitated by a Gel Doc XR System (Bio-Rad, Hercules, CA, U.S.A.).

**Glucose Take-Up** The cells were protected with 100 µM of insulin for 24 h, and refined with sans serum DMEM (5.5 mM Glucose, Gibco) for 3 h. To decide the impact of polydatin on glucose take-up in insulin-resistant cells, polydatin (10, 20, 40 µM) was included sans serum low glucose DMEM cells (5.5 mM glucose, Gibco). Next, the cells were brooded with 50 µM of 2-[1-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-amino]-2-deoxy-D-glucose (2-NBDG) (Invitrogen) and 1 µM of insulin for 60 min. Cells were then resuspended after transcription with 1 mL of phosphate buffered saline (PBS) (Shenggong, Shanghai, China) and mean fluorescence power was identified for 1.0×104 cells in the fluorescein isothiocyanate (FITC) channel by flow cytometry (EPICS XL, Beckman Coulter, U.S.A.).\textsuperscript{26,27} The cells were then seeded in a 96-well dark microtiter and fluorescence power was identified at Ex/Fx: 465/540 utilizing a microplate reader. All cells were contrasted with normal controls.

**Glucose Utilization** HepG2 cells were pretreated with
10, 20, and 40 µM of polydatin in DMEM without phenol red (25 mM glucose, Genom, Hangzhou, China) for 2h, and treated with 100 nM of insulin for 24h thereafter. After hatching with 100 nM of insulin for 4h, the medium was examined to quantify glucose fixations utilizing the glucose oxidation technique (Jiancheng, Nanjing, China). Finally, glucose utilization was computed by subtracting glucose fixation in the clear gathering (no cells, just medium) and standardized using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.28

Oil Red O Recoloring After treatment with polydatin or insulin, the intersecting cell monolayer was settled in 4% (w/v) paraformaldehyde for 10 min after washing with PBS, and then recolored with oil red O arrangement (Sigma) (6 sections of soaked oil red O color in isopropyl liquor +4 sections of refined water) for 30 min at room temperature. The arrangement was then evacuated and recolored with hematoxylin (Beyotime) for 5 min. Pictures were caught by microscope (Leica, German) after PBS washing.

Confocal Laser Examinining Fluorescence Microscopy (LSCM) HepG2 cells were refined on glass cover slips. After treatment, the cells were washed with PBS, settled for 30 min at room temperature with 4% (w/v) paraformaldehyde (Boster, Wuhan, China), permeabilized with 1% (v/v) Triton X-100 in PBS for 10 min at room temperature, and obstructed with goat serum for 1 h. After washing, the cells were harvested overnight in goat serum with hostile SREBP-1c immune response (1:50) and then hatched for 1 h with FITC-conjugated auxiliary immunizer (Goat against rabbit IgG labeled with Alexa Fluor ® 594, 1:1000, Invitrogen). The cover slips were mounted on glass slides with hostile to blur mounting media (Invitrogen), and pictures were gathered utilizing a Zeiss LSM 710 laser confocal fluorescence microscope (Carl Zeiss, Oberkochen, Germany). No fluorescence hybrid was observed between the channels, and pictures were gathered and consolidated independently utilizing fitting laser excitation wavelengths.

Statistical Investigation Information were expressed as mean±standard deviation (S.D.) and analyzed by Graphpad Prism 5.0 programming. Unpaired Student’s t-test performed correlations between the two gatherings. For multiple comparisons, data were analyzed by one-way ANOVA with post hoc multiple comparisons. Free analysis was performed in triplicate. p<0.05 was considered statistically significant.

RESULTS

The Impact of 100 nM Insulin on the Insulin Protection of HepG2 Cells Protein kinase B (Akt) is a crucial mediator of insulin-resistant glucose and lipid digestion. Under physiological conditions, Akt can be initiated by insulin and a few developmental factors. Akt is sensitive to insulin, and when cells are presented to insulin for long periods, Akt flagging becomes noticeably weaker and can prompt insulin protection.

Figure 2A demonstrates that phosphorylated Akt expanded following 10 min of treatment with 100 nM on HepG2 cells (p<0.05). To decide time impact Akt phosphorylation, 100 nM of insulin was connected to HepG2 cells for 10 min, and 6, 12, and 24h thereafter. Phosphorylation of Akt was observed to diminish time-conditionally. Compared to 10 min, phosphorylated Akt was fundamentally diminished when treated for 24 h (Fig. 2A, p<0.05).

Lieberthal et al. exhibited that Akt adds to the survival action of AMPK in refined proximal tubular cells.29) Similarly, we found that 100 nM insulin invigorated for 24 h diminished the phosphorylation of AMPK and HepG2 cells without insulin (Fig. 2B, p<0.05). Nucleoprotein of SREBP-1c is related to cholesterol generation. Figure 2C demonstrates that 100 nM insulin treated for 24 h altogether expanded the nucleoprotein of SREBP-1c (p<0.05). Therefore, insulin-resistant HepG2

![Fig. 2](image)

HepG2 cells were exposed to 100 nM of insulin for 10 min, 6, 12, 24 h or not as a control. Then the phosphorylation and total levels of Akt (A), AMPK (B), and nuclear and cytoplasm protein levels of SREBP-1c (C) of HepG2 Cell.
cells actuated by 100 nM insulin for 24 h were connected to this examination.

**Polydatin Enhances Glucose and Lipid Digestion**

Glucose take-up can be controlled by radioactive substances, including 2-deoxy-d-[3H] glucose or 2-deoxy-d-[14C] glucose. In any case, radioactive mixes can contaminate nature, represent a health risk to people, and cannot specifically exhibit glucose take-up of living cells. Recent research has indicated that HepG2 cells treated with fluorescent d-glucose simple 2-NBDG coupled with stream cytometry can recognize cell fluorescence force.

To investigate the role polydatin plays in controlling glucose in insulin-resistant HepG2 cells initiated by 100 nM insulin for 24 h, stream cytometry measured glucose take-up. Glucose oxidase techniques measured glucose and its change for glucose utilization. Figure 3A demonstrates that insulin impact for 1 h expanded glucose take-up essentially (p < 0.05). Notwithstanding, following 24 h, the take-up of glucose altogether diminished (p < 0.05). The 10 and 40 µM of polydatin and 1 µM of 5-aminimidazole-4-carboxamide riboside (AICAR) medicines altogether expanded glucose take-up (p < 0.05). Also, 10, 20, and 40 µM of polydatin and 1 µM of AICAR treatment significantly expanded glucose utilization (Fig. 3B, p < 0.05), which then decreased in the insulin protection display (p < 0.05). In this manner, these outcomes suggest that polydatin can diminish the insulin protection state of HepG2 cells by provoking glucose take-up in cells and potentiating glucose utilization.

To assess the role of polydatin on lipid control in insulin-resistant HepG2 cells actuated by 100 nM insulin for 24 h, oil red O recoloring was performed. The outcomes showed oil amassing in insulin-resistant assembly, which was hindered by polydatin and AICAR treatment (Fig. 4A). Consequently, this polydatin may play an important role in directing lipid digestion in insulin-resistant cells.

**The Component of Polydatin on Improving Glucose Digestion**

Glycogen synthase kinase (GSK)-β is a key chemical in hepatic glucose digestion that can hinder glycogen synthase movement by phosphorylation of glycogen amalgamation. Akt can phosphorylate GSK-3β at serine 9 to constrain movement and advance glycogen synthesis. The damaged phosphorylation action of Akt can weaken GSK-3β phosphorylation, promote GSK-3β action, and inhibit glycogen synthesis.

To investigate the system of polydatin on insulin protection, Western blot distinguished the phosphorylation levels of AMPK, Akt, and GSK-3β. Figures 5A–C showed that AMPK, Akt, and GSK-3β phosphorylation levels were clearly inhibited in insulin-resistant HepG2 cells than insulin treated cells after 10 min (p < 0.05). Polydatin elevated phosphorylated AMPK, Akt, and GSK-3β (p < 0.05) measurements conditionally. AICAR expanded phosphorylated AMPK and GSK-3β (p < 0.05). Additionally, AMPK, Akt, and GSK-3β protein levels were not observed to change. This demonstrated polydatin may expand GSK-3β phosphorylation and Akt or AMPK initiation, thereby advancing glycogen amalgamation and diminishing blood glucose. However, this strategy requires further examination.

**The Component of Polydatin on Improving Lipid Digestion**

SREBPs are characterized as essential helix-circle leucine zipper family interpretation factors integrated to endoplasmic reticulum film. SREBPs can situate to the Golgi device where they are severed and can then translocate and actuate target expression. Expanded nuclear SREBP-1c relates to liver lipogenic proteins and hepatic steatosis. LSCM and Western blot strategies distinguished the impact of polydatin on SREBP-1c. Figure 4C demonstrates that the nuclear red fluorescence of SREBP-1c altogether improved following 24 h of hatching with insulin, and decreased after the treatment of polydatin in 10, 20, 40 µM, and AICAR in 1 mM. Moreover, Western blot demonstrated that nuclear SREBP-1c protein levels were uniquely expanded in the insulin-resistant gathering (p < 0.01) and were protected after treatment with polydatin and AICAR (Fig. 4D, p < 0.05).

Figure 4E demonstrates that phosphorylated ACC levels were particularly diminished in HepG2 cells than in ordinary controls (p < 0.05). Polydatin at all dosages and AICAR expanded phosphorylated ACC levels (p < 0.05, p < 0.01). Interestingly, ACC levels were not observed to change. Moreover, low density lipoprotein receptor (LDLR) protein expression in typical HepG2 cells was expanded by treatment with 100 nM of insulin for 10 min (p < 0.01). LDLR protein levels in HepG2 cells presented to insulin for 24 h were diminished (p < 0.05). Polydatin treatment with 20 and 40 µM expanded LDLR ex-
pression (Fig. 4B, \( p < 0.05 \)).

These outcomes demonstrate that polydatin can generate the phosphorylation of ACC, diminish SREBP-1c, and increase the protein levels of LDLR. Accordingly, it is concluded that polydatin can decrease key qualities of lipogenesis and the age of triglycerides, alongside expanding the disposal of LDL to direct lipid digestion.

**DISCUSSION**

A cell model was applied to investigate the effect of polydatin on insulin resistance. We used 100 nm insulin over 24 h to treat HepG2 cells. We discovered that insulin significantly inhibited insulin-resistant Akt and AMPK pathways and increased nuclear SREBP-1c protein levels.

The Akt signal activated immediately when cells were activated by insulin for 10 min. However, when insulin was stimulated for long periods, insulin sensitivity was decreased, and the Akt signaling pathway was inhibited (Fig. 2A). Accordingly, these results certificate a successful insulin-resistant cell model. Lieberthal et al. reported AMPK inhibition in proximal tubular cells due to decreased phosphorylated Akt, thereby indicating...
that AMPK has a relationship with Akt phosphorylation. Bertrand et al.\textsuperscript{33)} reported that continuously stimulating AMPK in myocardial cells can Akt-dependently increase glucose take-up.\textsuperscript{33)} Overall, the double inhibition of AMPK and Akt is caused by insulin-resistant cells and the combined interaction of AMPK and Akt.

In vitro investigations were performed to observe the improvements of polydatin on glucose and lipid metabolism in low-dosages on HepG2 cells. The flow cytometry results demonstrated that insulin stimulated for 24 h significantly decreased insulin-resistant HepG2 cell glucose take-up. Ten and forty micromolar of polydatin and 1 mM of AICAR treatments significantly increased glucose take-up ($p<0.05$). In addition to glucose take-up, 10, 20, and, 40 $\mu$M of polydatin and 1 mM of AICAR treatments significantly increased glucose utilization ($p<0.05$). The oil O dye results demonstrated that polydatin reduced the lipid accumulation of the insulin-resistance cell model. Recently, Chen and Lan\textsuperscript{34)} have reported that polydatin treatment can activate AMPK protein and increase Sirt1 expression. Therefore, we further observed the extent to which experimental effects mediate the relationship with the AMPK signaling pathway.

The activated AMPK signaling pathway widely functions as a regulator. For example, Gilles\textsuperscript{35)} reported that AICAR-induced AMPK activation results in up-regulation of p-Akt (Ser473 and Thr308) and decreases p-mammalian target of rapamycin (mTOR) (Ser2448) expression and downstream signaling. Inhibition of AMPK using compound-C decreased p-Akt expression at both residues, indicating a central role for AMPK in Akt activation. Akt phosphorylates GSK-3$\beta$ at serine 9 and inhibits its activity, thereby further promoting glycogen synthesis.\textsuperscript{13,31)} In terms of lipid metabolism, ACC1 and ACC2 catalyze the carboxylation of acetyl-CoA to malonyl-CoA. Malonyl-CoA is a substrate for fatty acid synthase and can inhibit carnitine palmitoyltransferase-1, such that malonyl-CoA is a key molecule for regulating both the biosynthesis and oxidation of fatty acids. ACC1 and ACC2 are critical regulators of fatty acid synthesis and oxidation pathways.\textsuperscript{36)} AMPK phosphorylated ACC directly, thereby decreasing fatty acid in the mitochondria and reducing the rate of fatty acid oxidation. Moreover, AMPK interacts with and directly phosphorylates sterol regulatory element binding proteins (SREBP-1c and -2). AMPK can stimulate Ser372 phosphorylation, reduce SREBP-1c cleavage and nuclear translocation, and attenuate the expression of SREBP-1c target genes in hepatocytes incubated with high glucose, thereby reducing lipogenesis and lipid accumulation.\textsuperscript{32)}

AICAR is a widely used synthetic agonist of AMPK and is considered an adenosine analogue that can uptake cells by adenosine transportation, phosphorylation to 5-aminoimidazole-4-carboxamide-1-$\beta$-D-ribofuranosyl 5'-monophosphate (ZMP), and adenosine kinase. Accordingly, ZMP can activate the AMPK pathway by imitating the role of AMP.\textsuperscript{37)} Yashiro et al.\textsuperscript{38)} reported that AICAR increased the protein and mRNA levels of LDLR in hepatocytes, which accords with our results whereby AICAR significantly increased LDLR protein levels. However, they reported that this effect was a result of the Erk1/2 pathway.\textsuperscript{38)} Other experiments also have reported that resveratrol can augment LDLR protein levels independent of the AMPK pathway.\textsuperscript{39)} Proprotein convertase subtilisin/kexin type-9 (PCSK9) can bind to LDLR as a molecular chaperone to generate LDLR degradation.\textsuperscript{40)} As our

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**Fig. 5. The Effects of Polydatin on the Phosphorylation Levels of AMPK (A), Akt (B) and GSK-3$\beta$ (C) of Insulin-Resistant HepG2 Cells**

Cells were pretreated with polydatin (10, 20, 40 $\mu$m) and AICAR (1 mM) for 2 h, and then incubated with insulin (100 nM) for 24 h. And protein was extracted for immunoblotting after normal cell stimulated of 100 nM insulin for 10 min. Mean±S.D.; PD: polydatin, Ins: insulin. *$p<0.05$ vs. insulin resistance group; **$p<0.01$ vs. insulin resistance group; # $p<0.05$ vs. normal control group.
results suggest, this may be because polydatin can increase LDLR by downregulating PCSK9.41)

In summary, we found that polydatin increased AMPK activation, increased phosphorylated AMPK, Akt, and ACC, while decreasing nuclear protein levels of SREBP-1c and increasing LDLR expression. These results indicated that polydatin can protect the glucose metabolism by increasing phosphorylated AMPK, Akt, and GS-3β, as well as increasing the production of hepatic glycogen to regulate blood glucose. Polydatin can improve lipid metabolism by increasing phosphorylation levels of ACC, while decreasing nuclear protein levels of SREBP-1c to decrease the formation of cholesterol, and increase the protein levels of LDLR to promote elimination of LDL-cholesterol. The internal mechanisms of polydatin in the treatment of insulin resistance may be relevant for regulating the AMPK pathway and increasing LDLR expression.

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Conflict of Interest The authors declare no conflict of interest.

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