



RESEARCH ARTICLE

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SALVIANOLIC ACID B ATTENUATES GLUCOLIPOTOXICITY-INDUCED OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN AML12 HEPATOCYTES VIA MODULATING CRBN/AMPK SIGNALING

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ABSTRACT

Salvianolic acid B (SalB) is a major water-soluble phenolic compound with reported antioxidant and metabolic regulatory properties. We investigated its hepatoprotective effects in AML12 cells exposed to high glucose and palmitic acid (HG-PA), an in vitro model of diabetes-associated non-alcoholic fatty liver disease. SalB showed minimal cytotoxicity and significantly improved cell viability after HG-PA challenge. It reduced mitochondrial reactive oxygen species and 4-hydroxynonenal accumulation, indicating attenuation of oxidative stress and lipid peroxidation. SalB also restored MitoTracker fluorescence and intracellular ATP levels, consistent with improved mitochondrial function and cellular bioenergetics. HG-PA increased cereblon (CRBN) expression and suppressed AMPKα phosphorylation, whereas SalB partially reversed both changes. These findings suggest that SalB protects hepatocytes from glucolipotoxic injury by limiting oxidative damage, preserving mitochondrial function, and restoring CRBN-associated AMPK signaling.



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Key words: Salvianolic acid B, glucolipotoxicity, oxidative stress, mitochondrial function, cereblon (CRBN); AMP-activated protein kinase (AMPK).

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1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly termed non-alcoholic fatty liver disease (NAFLD), is the most common chronic liver disorder worldwide and is strongly associated with obesity and type 2 diabetes mellitus (T2DM) [1, 2]. More than half of patients with T2DM are estimated to have NAFLD/MASLD, and diabetes is associated with greater risks of steatohepatitis, advanced fibrosis, and adverse liver-related outcomes [3, 4]. Thus, diabetes-associated hepatic injury represents an important target for mechanistic investigation and therapeutic intervention.

A key mechanism linking diabetes to liver injury is glucolipotoxicity, caused by sustained exposure to excess glucose and free fatty acids. Palmitic acid, a major circulating saturated fatty acid, promotes oxidative stress, lipid peroxidation, mitochondrial dysfunction, endoplasmic reticulum stress, and hepatocyte injury [5, 6]. High glucose further potentiates palmitate-induced toxicity, making combined high-glucose and palmitate exposure a relevant in vitro model of diabetes-associated metabolic liver injury [5]. Mitochondrial dysfunction is central to this process because excessive reactive oxygen species generation and impaired ATP production compromise hepatocyte viability and metabolic homeostasis [2,6]. These disturbances are increasingly recognized as key drivers of progression from simple lipid accumulation to inflammatory and fibrotic liver disease, particularly in the setting of insulin resistance and T2DM. AMP-activated protein kinase (AMPK) is a key energy sensor governing hepatic lipid and energy metabolism. Cereblon (CRBN) negatively regulates AMPK, whereas CRBN deficiency enhances hepatic AMPK activity and improves metabolic homeostasis [7, 8]. However, the role of CRBN/AMPK signaling in hepatocyte glucolipotoxicity remains unclear.

Salvianolic acid B (SalB) is a major water-soluble polyphenolic constituent of *Salvia miltiorrhiza* Bunge (Danshen), a medicinal herb widely used in traditional Chinese medicine. Sal B has been reported to exert antioxidant, anti-inflammatory, anti-apoptotic, and anti-fibrotic effects in various experimental models. Previous studies have shown that SalB preserves mitochondrial function, attenuates liver fibrosis, inhibits hepatocyte ferroptosis, and improves experimental MASLD/MASH through mechanisms involving SIRT1/p53 and Piezo1-mediated calcium signaling [9-12]. Despite these findings, the protective effects of SalB under combined hyperglycemic and lipotoxic conditions, which closely resemble the metabolic stress associated with diabetes-related liver injury, remain incompletely characterized. In particular, how SalB influences oxidative damage, mitochondrial bioenergetics, and metabolic stress-responsive signaling in hepatocytes requires further investigation. Therefore, this study evaluated the effects of SalB in AML12 hepatocytes exposed to high glucose and palmitate and explored potential molecular targets that may contribute to its mechanism of action.

2. Materials and Methods

2.1. Cell lines and culture

Alpha mouse liver 12 (AML12) cells (ATCC, Manassas, VA, USA) were cultured in Dulbecco's modified Eagle's medium/Ham's F-12 (DMEM/F12) supplemented with 10% fetal bovine serum (FBS), insulin–transferrin–selenium (ITS), 40 ng/mL dexamethasone, and 1% penicillin–streptomycin. Cells were maintained at 37 °C in a humidified atmosphere containing 5% CO₂ and were subcultured before reaching complete confluence. Cells within a consistent passage range were used throughout the experiments.

2.2. Main reagents

The reagents used in the study including Salvianolic acid B (purity ≥98%, HY-N1362, MedChemExpress), D-Plus™ CCK cell viability assay kit (CCK-3000, Dongin, Korea), ATP assay (ab83355, Abcam), 4-hydroxynonenal (4-HNE) assay kits (ab238538, Abcam), MitoTracker (M22426) and MitoSOX Red (M36008) were purchased from Thermo Fisher. Primary antibodies against cereblon (CRBN), phospho-AMPKα (Thr172), total AMPKα, and HSP90 were obtained from Cell Signaling with catalog number: 71810S, 2535S, 5831S, and 4877S, respectively. Horseradish peroxidase (HRP)-conjugated secondary antibody (LF-QC0101) was obtained from Abfrontier.

2.3. Cell treatment

To establish an in vitro model of diabetes-associated hepatocellular glucolipotoxicity, AML12 cells were exposed to high glucose (HG; 35 mM) and PA (200 μ M) for 24h as previously described [13]. Control cells received the corresponding vehicle treatment. The cytotoxicity of SalB was initially evaluated over a concentration range of 0 - 400 μ M. To determine its protective concentration, HG-PA-treated cells were exposed to 5, 10, or 20 μ M SalB. The optimal SalB concentration for subsequent mechanistic experiments is selected based on the best cell survival results. The principal experimental groups were: (1) control, (2) HG-PA, and (3) HG-PA + 10 μ M SalB. SalB was administered concurrently with HG-PA exposure.

2.4. Cell viability

Cell viability was determined using the D-Plus CCK assay. AML12 cells were seeded into 96-well plates at 5×10^3 cells and allowed to adhere overnight. For the cytotoxicity experiment, cells were treated with SalB at 0, 5, 10, 20, 40, 80, 100, 200, or 400 μ M. Following treatment, D-Plus CCK reagent was added to each well according to the manufacturer's instructions, and cells were incubated at 37 °C for 1h. Absorbance was measured at 450 nm using a microplate reader. Cell viability was calculated relative to the untreated control and expressed as a percentage of control.

2.5. ATP level assay

Intracellular ATP levels were determined using a commercial ATP assay kit according to the manufacturer's protocol. Following treatment, AML12 cells were collected and lysed under conditions recommended for the assay. Cell lysates were centrifuged to remove insoluble material, and ATP content in the supernatant was measured using colorimetric detection. ATP concentrations were calculated from a standard curve and normalized to total cellular protein content, determined using the BCA protein assay. ATP levels were expressed as nmol/mg protein.

2.6. Measurement of 4-HNE levels

Lipid peroxidation was assessed by measuring cellular 4-HNE levels using a commercial kit. After treatment, cells were harvested, lysed, and centrifuged, and the resulting supernatants were analyzed according to the manufacturer's instructions. Absorbance was measured using a microplate reader at the wavelength specified by the assay manufacturer. 4-HNE concentrations were determined from a standard curve, normalized to total protein content, and expressed as μ g/mg protein.

2.7. Mito Tracker staining

Mitochondrial status was evaluated using MitoTracker staining. Following treatment, AML12 cells cultured on imaging plates were washed with pre-warmed phosphate-buffered saline (PBS) and incubated with 150 nM MitoTracker at 37 °C for 30 min in the dark. Cells were then washed with PBS and counterstained with DAPI to visualize nuclei. Fluorescence images were acquired using a confocal microscope under identical acquisition settings for all experimental groups. MitoTracker fluorescence intensity was quantified using ImageJ software and normalized to the control group.

2.8. MitoSOX red staining

Mitochondrial reactive oxygen species (ROS) production was assessed using MitoSOX Red. Following the indicated treatments, AML12 cells were washed with pre-warmed PBS and incubated with 200 nM MitoSOX Red at 37 °C for 30 min in the dark. Excess probe was removed by washing with PBS. Fluorescence images were acquired immediately using a confocal microscope with identical imaging parameters among groups. MitoSOX fluorescence intensity was quantified using ImageJ and expressed as fold change relative to the untreated control.

2.9. Western blot analysis

Following treatment, AML12 cells were washed with ice-cold PBS and lysed in RIPA buffer supplemented with protease and phosphatase inhibitors. Cell lysates were centrifuged at 12000 rpm for 15 min at 4 °C, and protein concentrations were determined using a BCA protein assay. Equal amounts of protein were separated by SDS-polyacrylamide gel electrophoresis and transferred onto nitrocellulose membranes. Membranes were blocked with 5% skim milk in Tris-buffered saline containing 0.1% Tween-20 (TBST) for 1 h at room temperature and subsequently incubated overnight at 4 °C with primary antibodies. After washing with TBST, membranes were incubated with the appropriate HRP-conjugated secondary antibodies for 1 h at room temperature. Protein bands were visualized using enhanced chemiluminescence and captured with a chemiluminescence imaging system. Band intensities were quantified using ImageJ software.

2.10. Statistical analysis

All quantitative in vitro experiments were performed in n=3-5 independent experiments. Data are presented as the mean $\pm$ SD. Statistical analyses were performed using GraphPad Prism version 8. Comparisons between multiple groups were performed using one-way analysis of variance (ANOVA) followed by an appropriate multiple-comparison Tukey's test. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. SalB protects AML12 hepatocytes against HG-PA-induced reduction of cell viability

The cytotoxicity of SalB was first evaluated in AML12 cells over a concentration range of 0-400 μ M. SalB alone did not significantly affect cell viability at any concentration tested, indicating minimal cytotoxicity under the experimental conditions (Fig. 1A). Exposure to high glucose and palmitic acid (HG-PA) significantly reduced cell viability compared with the control group ($P < 0.0001$). Treatment with 5 μ M SalB did not significantly improve viability, whereas 10 and 20 μ M SalB significantly attenuated the HG-PA-induced reduction in cell viability (both $P < 0.01$). No significant difference was observed between the 10 and 20 μ M SalB groups (Fig. 1B). Accordingly, 10 μ M SalB was selected for subsequent experiments.

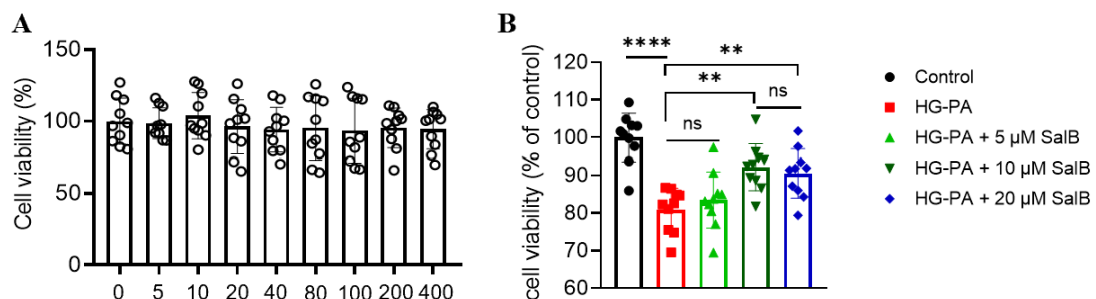


Figure 1. The effect of SalB on the viability of AML12 liver cells with and without HG-PA supplementation. (A) Effect of salvianolic acid B (SalB) on AML12 cell viability over the indicated concentration range. (B) Effect of SalB treatment on cell viability in AML12 hepatocytes exposed to high glucose and palmitate (HG-PA). Data are presented as mean $\pm$ SD, n=5 independent experiments. Statistical significance is indicated by ** $P < 0.01$, **** $P < 0.0001$, ns, not significant.

3.2. SalB attenuates HG-PA-induced mitochondrial oxidative stress and lipid peroxidation

Mitochondrial ROS production was assessed using MitoSOX Red staining. HG-PA exposure markedly increased MitoSOX fluorescence compared with control cells ($P < 0.0001$), indicating enhanced mitochondrial oxidative stress. SalB treatment significantly reduced the HG-PA-induced increase in MitoSOX fluorescence ($P < 0.01$) (Fig. 2A, B). Consistent with increased oxidative damage, cellular 4-hydroxynonenal (4-HNE), a marker of lipid peroxidation, was significantly elevated following HG-PA exposure ($P < 0.001$). SalB significantly decreased 4-HNE levels compared with the HG-PA group ($P < 0.05$) (Fig. 2C). These findings indicate that SalB attenuates oxidative stress and lipid peroxidation during hepatocellular glucolipotoxicity.

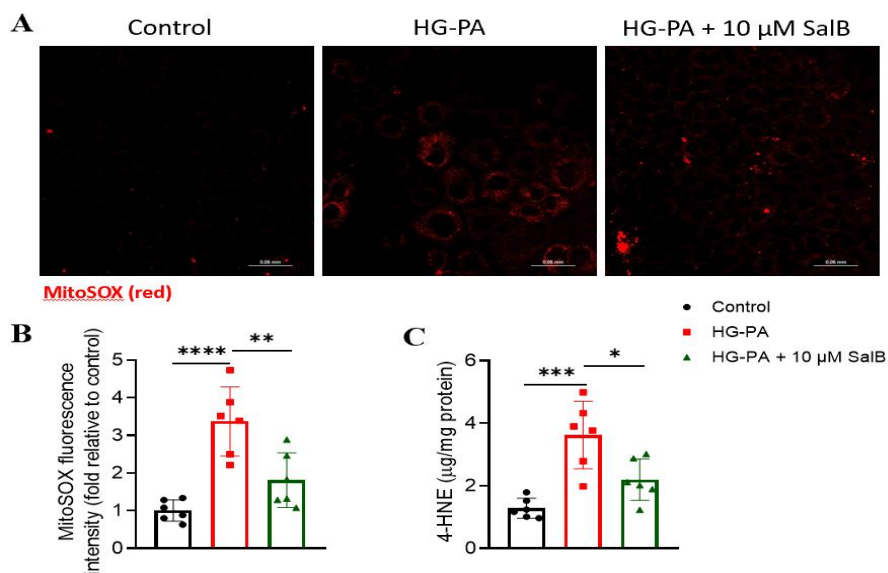


Figure 2. Effects of SalB on mitochondrial ROS generation and lipid peroxidation in AML12 cells under HG-PA condition.

(A) Representative fluorescence images of mitochondrial reactive oxygen species (ROS) detected using MitoSOX Red staining. (B) Quantification of MitoSOX fluorescence intensity. (C) Cellular 4-hydroxynonenal (4-HNE) levels as an index of lipid peroxidation. Data are presented as mean $\pm$ SD, $n=3$ independent experiments. Statistical significance is indicated by * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, and **** $P < 0.0001$.

3.3. SalB ameliorates HG-PA-induced mitochondrial dysfunction and ATP depletion

MitoTracker staining was used to evaluate mitochondrial status. HG-PA markedly reduced MitoTracker fluorescence intensity compared with control cells ($P < 0.0001$). Treatment with 10 μ M SalB significantly restored MitoTracker fluorescence relative to the HG-PA group ($P < 0.01$) (Fig. 3A, B). HG-PA exposure also significantly decreased intracellular ATP levels compared with the control group ($P < 0.001$), consistent with impaired cellular bioenergetics. SalB treatment significantly increased ATP levels compared with HG-PA alone ($P < 0.05$), although the values remained below those of untreated controls (Fig. 3C). Together, these results suggest that SalB partially preserves mitochondrial function and energy production under HG-PA-induced metabolic stress.

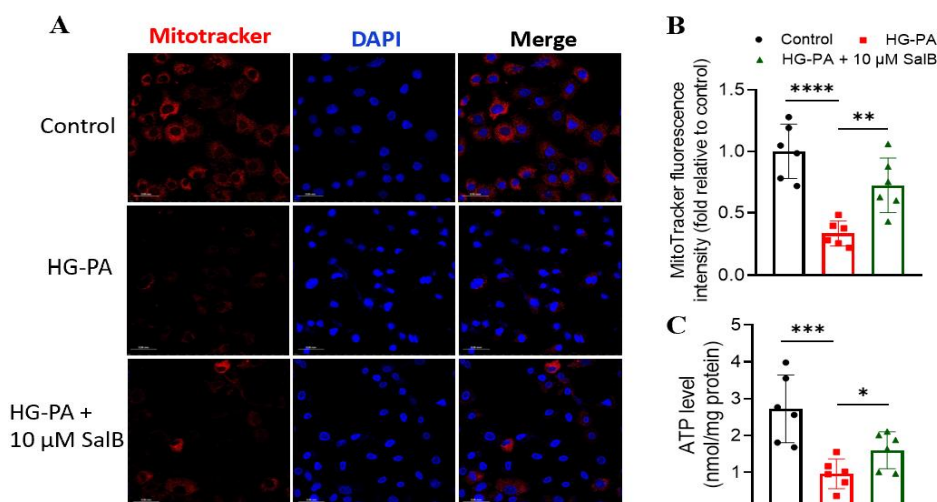


Figure 3. Effects of SalB on mitochondrial status and cellular ATP levels in AML12 cells under HG-PA condition.

(A) Representative MitoTracker fluorescence images showing mitochondrial staining. (B) Quantification of MitoTracker fluorescence intensity. (C) Intracellular ATP levels in AML12 hepatocytes. Data are presented as mean $\pm$ SD, $n=3$ independent experiments. Statistical significance is indicated by * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, and **** $P < 0.0001$.

3.4. SalB modulates CRBN/AMPK signaling in HG-PA-treated AML12 cells

To examine signaling pathways potentially associated with the protective effects of SalB, CRBN expression and AMPK phosphorylation were analyzed by Western blotting. HG-PA significantly increased CRBN protein expression compared with the control group ($P < 0.01$). SalB treatment significantly reduced CRBN expression relative to HG-PA-treated cells ($P < 0.05$) (Fig. 4A, B). In contrast, phosphorylated AMPK α was significantly reduced by HG-PA exposure ($P < 0.01$). Treatment with SalB significantly increased AMPK α phosphorylation compared with the HG-PA group ($P < 0.05$) (Fig. 4A, C). Thus, the protective effects of SalB against HG-PA-induced hepatocellular injury were accompanied by suppression of CRBN upregulation and recovery of AMPK activation. Collectively, these findings demonstrate that SalB protects AML12 hepatocytes against HG-PA-induced glucolipotoxic injury. This protection is characterized by improved cell viability, reduced mitochondrial ROS and lipid peroxidation, preservation of mitochondrial function and ATP production, and normalization of CRBN-associated AMPK signaling.

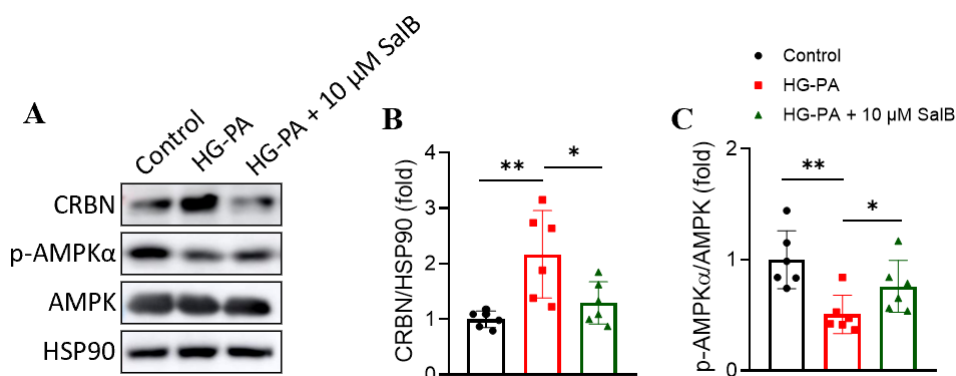


Figure 4. Effects of SalB on CRBN expression and AMPK phosphorylation in AML12 cells.

(A) Representative Western blot images of cereblon (CRBN), phosphorylated AMPK α (p-AMPK α), total AMPK α , and HSP90. (B) Densitometric analysis of CRBN protein expression normalized to HSP90. (C) Densitometric analysis of AMPK α phosphorylation. Data are presented as mean $\pm$ SD, $n=3$ independent experiments. Statistical significance is indicated by * $P < 0.05$, ** $P < 0.01$.

4. Discussion

This study demonstrates that salvianolic acid B (SalB) protects AML12 hepatocytes against high glucose–palmitate (HG-PA)-induced glucolipotoxic injury. SalB improved cell viability, reduced mitochondrial reactive oxygen species (ROS) and 4-hydroxynonenal (4-HNE), preserved mitochondrial status and ATP production, and was associated with decreased cereblon (CRBN) expression and restoration of AMPK phosphorylation.

Glucolipotoxicity is a major mechanism linking diabetes to metabolic liver injury. High glucose can exacerbate palmitate-induced hepatotoxicity through oxidative, metabolic, and integrated stress responses [5, 6]. Consistent with this concept, HG-PA markedly reduced AML12 cell viability in the present study. SalB significantly attenuated this loss of viability, indicating protection against combined hyperglycemic and lipotoxic stress.

Oxidative stress and mitochondrial dysfunction are central features of MASLD progression [2, 6]. HG-PA increased mitochondrial ROS and 4-HNE while reducing MitoTracker fluorescence and ATP levels, indicating oxidative damage and impaired cellular bioenergetics. SalB significantly reversed these alterations. These findings agree with previous studies showing that SalB preserves mitochondrial function and limits oxidative injury [9]. SalB has also been reported to inhibit hepatocyte ferroptosis and ameliorate experimental liver fibrosis and MASH [10, 11]. More recently, SalB improved experimental MASLD by suppressing Piezo1-mediated mitochondrial Ca^{2+} overload, oxidative stress, and metabolic dysfunction [12]. Together, these observations support mitochondrial and redox homeostasis as important components of SalB-mediated hepatoprotection.

A notable finding of this study was the reciprocal regulation of CRBN and AMPK. CRBN is a negative regulator of AMPK, and CRBN deficiency enhances hepatic AMPK activity and improves metabolic

homeostasis [7]. Mechanistically, CRBN can inhibit AMPK through ubiquitin-dependent degradation of the AMPK γ subunit [8]. In the present study, HG-PA increased CRBN expression and reduced AMPK phosphorylation, whereas SalB decreased CRBN and restored AMPK phosphorylation. This pattern suggests that modulation of CRBN-associated AMPK signaling may contribute to the metabolic protective effects of SalB. However, these findings demonstrate association rather than direct causality. CRBN knockdown or overexpression and pharmacological manipulation of AMPK will be required to establish a causal SalB–CRBN–AMPK pathway.

This study has several limitations. The study was restricted to AML12 cells, and mitochondrial function was assessed indirectly using MitoTracker staining and ATP levels. Additional analyses of mitochondrial respiration, membrane potential, lipid accumulation, and fatty acid oxidation, together with primary hepatocyte and in vivo validation, would strengthen the mechanistic conclusions.

5. Conclusion

SalB attenuates HG-PA-induced hepatocellular glucolipotoxicity by reducing oxidative stress and lipid peroxidation while preserving mitochondrial function and cellular ATP levels. These effects are accompanied by suppression of CRBN upregulation and recovery of AMPK phosphorylation. The findings identify CRBN-associated AMPK signaling as a potential mechanism underlying SalB-mediated hepatoprotection and support further investigation of SalB as a candidate therapeutic strategy for diabetes-associated metabolic liver disease.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-Assisted Technologies

The authors declare that no artificial intelligence (AI) was used to make any data and write the manuscript. The authors only used ChatGPT in order to check spelling, refine English grammar, and improve the overall readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content and integrity of the publication.

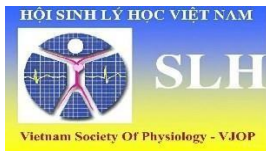
Author Contributions

Trong Kha Pham was responsible with the conceptualization and study design. Bich Thi Pham, Yen Thi Hai Ngo, Phuong Thi Thu Luu and Trong Kha Pham contributed to perform experiments, data analysis. Thu Thi Vu, Thuong Thi Bui, Trong Kha Pham contributed to make interpretation of results, preparing figures, drafting the manuscript, editing and critical review of the manuscript, and final approval of the manuscript.

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AXIT SALVIANOLIC B LÀM GIẢM STRESS OXY HÓA VÀ RỐI LOẠN CHỨC NĂNG TY THỂ DO ĐỘC TÍNH GLUCOSE-LIPID GÂY RA TRONG TẾ BÀO GAN AML12 THÔNG QUA ĐIỀU HÒA TÍN HIỆU CRBN/AMPK

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TÓM TẮT

Axit salvianolic B (SalB) là một hợp chất phenolic tan trong nước, được ghi nhận có đặc tính chống oxy hóa và điều hòa chuyển hóa. Chúng tôi đã nghiên cứu tác dụng bảo vệ gan của hợp chất này trên tế bào gan AML12 được xử lý bằng glucose và axit palmitic nồng độ cao (HG-PA), một mô hình *in vitro* mô phỏng bệnh gan nhiễm mỡ không do rượu liên quan đến đái tháo đường. Kết quả cho thấy SalB thể hiện độc tính tế bào không đáng kể và làm tăng đáng kể khả năng sống của tế bào sau khi tiếp xúc với HG-PA. SalB làm giảm các gốc oxy hóa hoạt động (ROS) trong ty thể và sự tích tụ 4-hydroxynonenal, cho thấy khả năng làm giảm stress oxy hóa và quá trình peroxy hóa lipid. SalB cũng phục hồi cường độ huỳnh quang MitoTracker và hàm lượng ATP nội bào, phù hợp với sự cải thiện chức năng ty thể và chuyển hóa năng lượng của tế bào. HG-PA làm tăng biểu hiện cereblon (CRBN) và ức chế quá trình phosphoryl hóa AMPK α , trong khi SalB đảo ngược một phần cả hai thay đổi này. Những phát hiện trên cho thấy SalB bảo vệ tế bào gan khỏi tổn thương do độc tính glucose-lipid bằng cách hạn chế tổn thương oxy hóa, duy trì chức năng ty thể và khôi phục tín hiệu AMPK liên quan đến CRBN.

Từ khóa: Axit Salvianolic B, độc tính glucose-lipid, stress oxy hóa, chức năng ty thể, cereblon (CRBN), AMP-activated protein kinase (AMPK)