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Isobavachromene ameliorates insulin resistance via inactivating the MAPK/NF-κB signaling pathway

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ABSTRACT

Inflammation caused by obesity, particularly in adipose tissue and the liver, can lead to insulin resistance (IR) and trigger type 2 diabetes mellitus (T2DM). It is crucial to identify therapeutic agents that alleviate IR by reducing inflammation. Here, we report that isobavachromene (IB), a flavonoid derived from *Psoralea corylifolia* Linn., ameliorates IR in 3T3-L1 adipocytes by inhibiting the mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway. We first found that IB could promote glucose uptake in 3T3-L1 adipocytes by activating the phosphoinositide 3-kinase (PI-3K)/protein kinase B (Akt) signaling pathway and was more effective than the positive control sodium orthovanadate at concentrations ranging from 25 to 100 μmol/L. Additionally, IB inhibited RAW264.7 macrophage infiltration into 3T3-L1 adipocytes and suppressed the secretion of inflammatory factors from RAW264.7 macrophages, as well as the phosphorylation levels of key proteins (NF-κB p65, extracellular-signal-regulated kinase 1/2 (ERK1/2), Jun N-terminal kinase (JNK), and mitogen-activated protein kinase 38 (p38)) in the NF-κB and MAPK signaling pathways. In summary, IB improves glucose uptake in IR adipocytes, activates the PI-3K/Akt signaling pathway, inhibits the JNK and NF-κB inflammatory signaling pathways, and reduces adipocyte inflammation, thereby improving of IR in 3T3-L1 adipocytes.

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1. Introduction

Insulin, as an important bioactive substance, plays a crucial role in energy production, metabolism, and cell survival and proliferation in both peripheral and central tissues of the human body, while insulin resistance (IR) contributes to the development and progression of type 2 diabetes mellitus (T2DM)[1-3]. Obesity is a major driver of IR in humans worldwide and can also lead to an increase in the prevalence of T2DM[4]. Importantly, inflammation caused by obesity, especially when it occurs in adipose tissue and the liver, leads to IR[5]. As a key target tissue for insulin, chronic inflammation in adipose tissue is a central factor contributing to the development and progression of IR[6]. Previous studies have demonstrated the significance of macrophage-mediated inflammation as a cause of IR[7-8]. Hence, macrophages and adipocytes are ideal models for *in vitro* studies aimed at improving insulin sensitivity.

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In recent years, efforts have been made to develop natural products into insulin sensitizers for the treatment of obesity or T2DM, and compounds isolated from natural products often exhibit multi-target effects to improve IR[9-10]. *Psoralea corylifolia* Linn., a traditional Chinese medicine (TCM), has been shown to have anti-inflammatory[11], cardiovascular protective[12] and hypoglycemic effects[13], showing better pharmacological activities[14]. Therefore, we isolated isobavachromene (IB) from *P. corylifolia*, a flavonoid that has been reported to have antibacterial activity[15], but whether and how IB improves glucose homeostasis and IR is still unknown. In this study, we investigated the effects of IB on glucose uptake in 3T3-L1 adipocytes with IR and on inflammation in RAW264.7 and 3T3-L1 adipocytes, respectively, to explore the mechanism of action of IB by reducing the adipocyte inflammatory response and thus improving IR.

2. Materials and methods

2.1 Materials

IB isolated and purified from *P. corylifolia* (purity > 95%) by the National R&D Center for Edible Fungus Processing Technology (China). 3-Isobutyl-1-methylxanthine (IBMX) and dexamethasone (Dex) were purchased from Sigma-Aldrich (USA) and detailed chemical information is listed in Table S1. Antibodies are listed in Table S2.

2.2 Cell culture

The 3T3-L1 preadipocytes and RAW264.7 macrophages were purchased from the cell bank of the Chinese Academy of Sciences (Shanghai, China). The cells were maintained in DMEM medium (with a mixture of 10% neonatal bovine serum and 1% penicillin) and placed in an incubator at 37 ℃ and 5% CO_2. The cells could be passaged when the confluence reached about 80%. 3T3-L1 cells were induced to mature into adipocytes and used to establish an IR model as described by Zhang et al.[16]. After confirming the induced differentiation into mature adipocytes, 1 μmol/L Dex was administered for 72 h. A blank control group, model group, positive control group, and drug treatment group were established. Sodium orthovanadate (Van, 10 μmol/L) served as the positive control; the drug treatment group was given different concentrations of IB, and the cells were collected after 48 h. For the inflammation model in RAW264.7 macrophages, the IB-treated group was pretreated by adding different concentrations of IB for 1 h, and then lipopolysaccharide (LPS, 1 μg/mL) was added concurrently with the model group for 24 h. Tumor necrosis factor alpha (TNF-α) was used to establish the inflammation model in 3T3-L1 adipocytes, and 3T3-L1 adipocytes and RAW264.7 macrophages were co-cultured and separated by a Transwell membrane, based on previously published methods[17].

2.3 Cell viability

After treatment of 3T3-L1 preadipocytes or RAW264.7 macrophages with different concentrations of IB (400, 200, 100, 50, and 25 μmol/L) for 24 h, the cells were incubated for 4 h with MTT solution (10 μL) protected from light. The medium was then discarded, and dimethyl sulfoxide (DMSO) (100 μL) was added to dissolve the blue-purple crystals. The samples were incubated at 37 ℃ for 10 min, and the absorbance was measured at 490 nm using an enzyme marker.

2.4 Western blot analysis

After lysing the cells using RIPA buffer for 30 min, the lysates were centrifuged at 12 000 r/min for 10 min at 4 ℃ and then subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) using polyacrylamide gels. Western blot analysis was performed as described previously[18]. Immunoblotting was conducted using specific antibodies to assess the expression of different proteins.

2.5 Quantitative real time-polymerase chain reaction (qPCR)

Total RNA from cells was extracted with TRIzol, gDNA was removed using a kit (TaKaRa), and the RNA was reverse transcribed to cDNA[19]. qPCR analysis was performed using TB Green® Premix Ex *Taq*™ II (Tli RNaseH Plus) in a gradient PCR detection system (MyCycler™ Thermal Cycler), and mRNA expression was normalized to *GAPDH*. The primer sequences are listed in Table S3.

2.6 Immunofluorescence

RAW264.7 macrophages were washed in PBS and fixed with 4% paraformaldehyde for 30 min, followed by permeabilization with 0.5% Triton X-100 for 15 min. Cells were blocked with 10% goat serum for 1 h at room temperature and then incubated overnight at 4 ℃ with the primary antibody (nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) p65). After washing with PBS, the cells were incubated with an Alexa Fluor-coupled secondary antibody for 2 h at room temperature and protected from light. Images were captured using a laser confocal fluorescence microscope (Nikon A1R/STORM).

2.7 Protein-ligand docking

The docking process was performed on the Sybyl X2.1.1 operating platform using the ligand simulation (docking) tool SUEFLEX DOCK. Firstly, the insulin receptor IR (PDB ID: 5KQV) was used as the target protein and IB as the ligand, with LEU36, LEU62, PHE64, PHE88, VAL94, and PHE96 as the critical active sites. Protein flexible docking was employed to determine the potential gradient and to perform computerized docking simulations. The drug-protein interaction analysis was performed based on the score and configuration of docking.

2.8 Statistical analysis

All experimental data are expressed as the mean ± standard deviation (SD) and were analyzed using SPSS 19.0. Multiple comparisons were assessed by one-way ANOVA with Tukey's tests. Statistical significance was defined as $P < 0.05$ (* or $^{\#}$), $P < 0.01$ (** or $^{\#\#}$), and $P < 0.001$ (*** or $^{\#\#\#}$).

3. Results

3.1 IB ameliorates IR in 3T3-L1 adipocytes

To determine whether IB (Fig. 1A) can ameliorate IR, we first assessed its effectiveness and mechanism in 3T3-L1 adipocytes. The MTT assay revealed that IB was not cytotoxic at concentrations ranging from 25 to 100 μmol/L (Fig. 1B). After successfully establishing IR in 3T3-L1 adipocytes, we found that IB significantly promoted the glucose uptake capacity of these adipocytes (Fig. 1C). Additionally, IB significantly enhanced GLUT4 transport, which is considered one of the primary manifestations of IR in the body, as indicated by increased GLUT4 protein expression levels (Fig. 1D), and IB was found to be superior to the positive control Van. Furthermore, we predicted that IB binds well to the insulin receptor at the sites Arg118 and Phe64 through molecular docking (Figs. S1A, B). To elucidate the glucose-lowering mechanism of IB in adipocytes, we discovered that IB activated the central link of the insulin pathway, specifically the IRS-1/PI-3K/Akt axis, and significantly increased the expression of PI-3K (P110α) and the phosphorylation levels of IRS-1 and Akt by Western blot, with the most effective concentration being 50 μmol/L (Fig. 1E). To further validate this result, we used the pathway-specific inhibitor Wortmannin (Wort) and examined the expression levels of PI-3K (P110α) and Akt (Fig. 1F). The results confirmed that IB could ameliorate IR in 3T3-L1 adipocytes by activating the PI-3K/Akt signaling pathway.

3.2 Effect of IB on LPS-induced inflammation in RAW264.7 macrophages

Adipose tissue disorders and IR are often accompanied by a chronic inflammatory state[20]. Therefore, we further investigated the anti-inflammatory effects of IB using a model of LPS-induced inflammation in RAW264.7 macrophages. The MTT assay revealed that IB was not cytotoxic at concentrations ranging from 25 to 100 μmol/L (Fig. 2A). We found that IB significantly reduced the secretion of nitric oxide (NO), a signature molecule of M1 macrophages (Fig. 2B), and inducible nitric oxide synthase mRNA (*iNOS*, Fig. 2C) at a dose of 50 μmol/L. In addition, increased production of the inflammatory factor TNF-α has an important effect on the generation of IR in obese individuals[21], and we found that IB significantly reduced both the secretion capacity (Fig. 2D) and transcription level (Fig. 2E) of TNF-α. Moreover, interleukin-6 (IL-6) (Figs. 2F, G) and IL-1β (Figs. 2H, I), key molecules in the cytokine storm, were also significantly reduced by IB. All the above results demonstrated the favorable anti-inflammatory effect of IB in RAW264.7 macrophages.

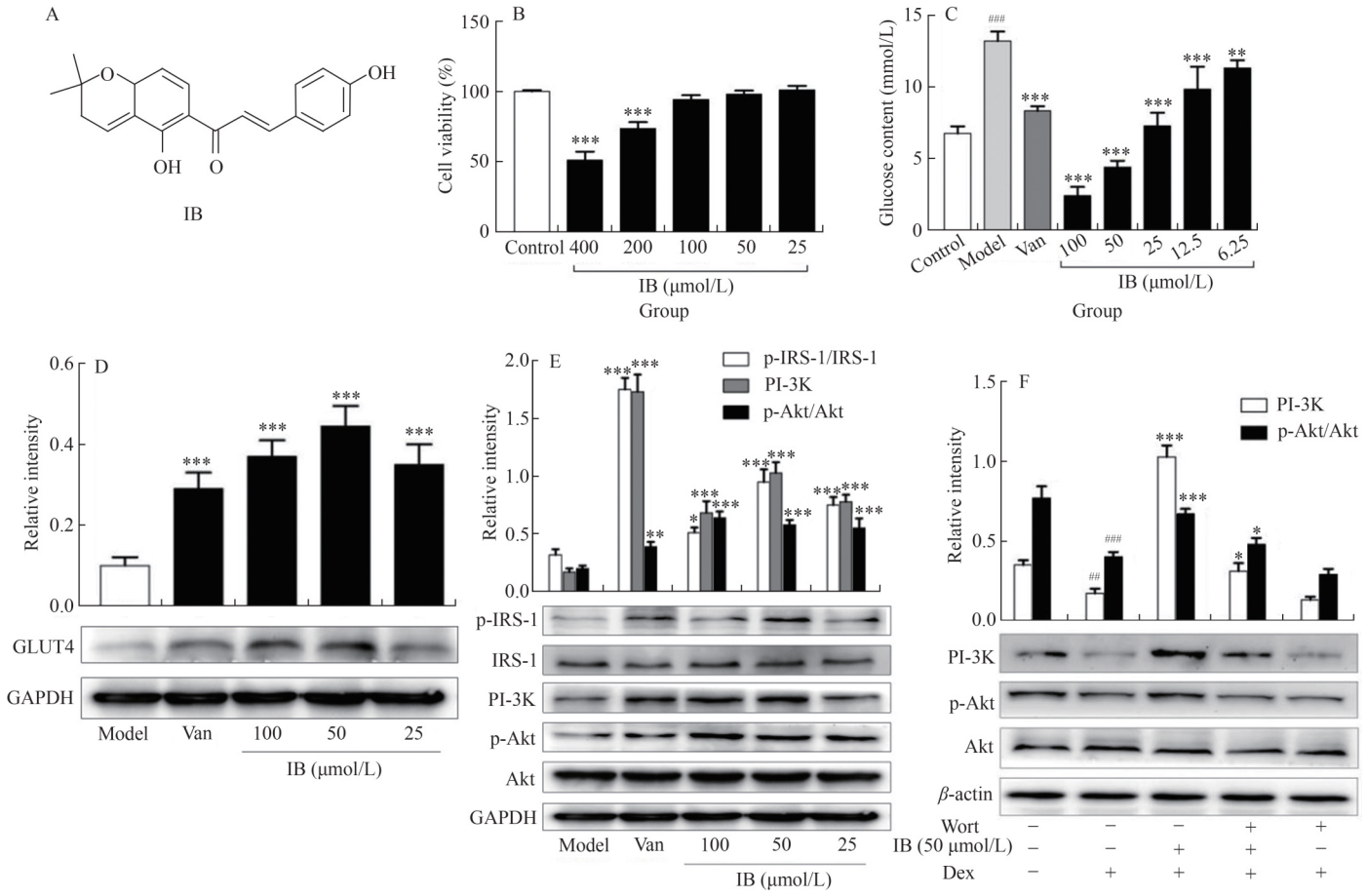


Fig. 1 IB ameliorates IR in 3T3-L1 adipocytes via the IRS-1/PI-3K/Akt signaling pathway. (A) Chemical structure of IB. (B) Effect of IB on the viability of 3T3-L1 preadipocytes ($n = 3$). (C) Effect of IB on glucose content in the supernatant of 3T3-L1 adipocytes ($n = 3$). (D) Western blot analysis was used to detect the effect of IB on glucose transporter protein (GLUT4) ($n = 3$). (E) Effect of IB on IRS-1/PI-3K/Akt-related protein expression ($n = 3$). (F) Effect of IB on the expression of PI-3K/Akt signaling pathway-related proteins after the action of the pathway inhibitor Wort (100 nmol/L) ($n = 3$). Data expressed as mean ± SD. $^{###}P < 0.001$, $^{##}P < 0.01$ *vs.* control group; $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ *vs.* model group.

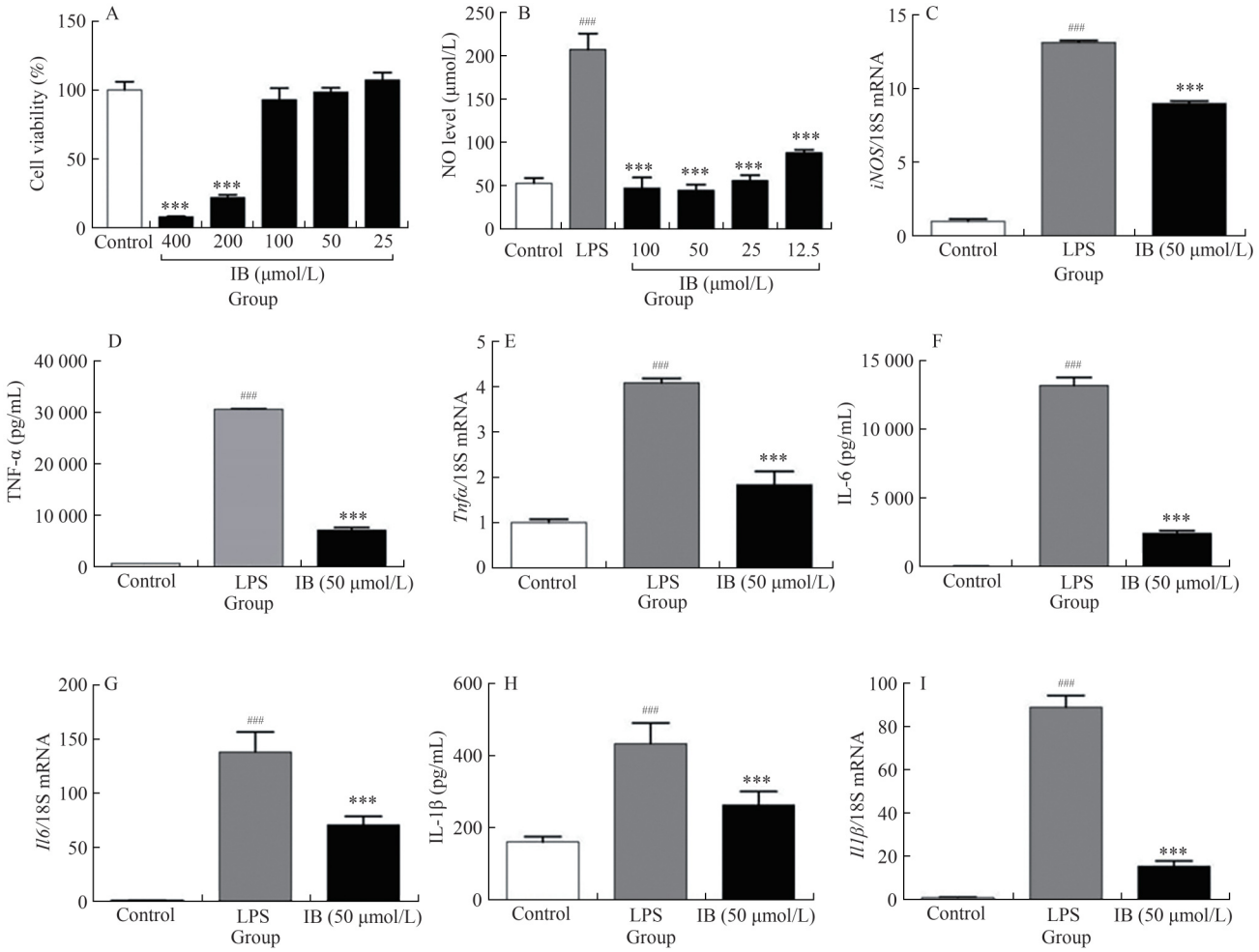


Fig. 2 Effect of IB on LPS-induced inflammation in RAW264.7 macrophages. (A) Effect of IB on the viability of RAW264.7 macrophages. (B) Effect of IB on NO secretion in RAW264.7 macrophages by nitrate reductase assay. (C) qPCR to detect the effect of IB on *iNOS* expression in RAW264.7 macrophages. (D, E) Effect of IB on the secretion of TNF-α and its mRNA transcription in RAW264.7 macrophages. (F, G) Effect of IB on the secretion of IL-6 and its mRNA transcription in RAW264.7 macrophages. (H, I) Effect of IB on the secretion of IL-1β and its mRNA transcription in RAW264.7 macrophages. Data expressed as mean ± SD, $n = 3$. $^{###}P < 0.001$ *vs.* control group; $^{***}P < 0.001$ *vs.* LPS group.

3.3 IB inhibits inflammation in RAW264.7 macrophages via MAPK/NF-κB signaling pathways

It has been conclusively demonstrated that mitogen-activated protein kinase (MAPK) and NF-κB play important roles in the inflammatory stress response[22-23]. Based on the determination that IB has favorable anti-inflammatory effects, we sought to elucidate its anti-inflammatory mechanisms. By Western blot, we found that IB treatment significantly inhibited LPS-induced phosphorylation of p38 MAPK, extracellular signal-regulated kinase (ERK), and C-Jun N-terminal kinase (JNK) proteins in RAW264.7 macrophages (Fig. 3A). Additionally, elevated TNF-α levels suggest that NF-κB can activate inflammatory genes through the nuclear translocation of the p65 component of the complex[24]. Therefore, we further investigated the anti-inflammatory properties of IB on the NF-κB signaling pathway. We observed that IB significantly inhibited the phosphorylation of NF-κB (Fig. 3B) in RAW264.7 macrophages, and we also noted that IB significantly inhibited the nuclear translocation of NF-κB as shown by laser confocal microscopy (Fig. 3C). These results suggest that IB inhibits LPS-induced inflammation by suppressing MAPK/NF-κB signaling in RAW264.7 macrophages.

3.4 IB ameliorated IR due to inflammation in 3T3-L1 adipocytes

We next aimed to clarify the causal relationship between inflammation and IR in 3T3-L1 adipocytes. We first used inverted microscopy to capture images of Transwell chambers, observed the migration of RAW264.7 macrophages to adipocytes, and found that IB treatment inhibited the infiltration of RAW264.7 macrophages into adipocytes (Fig. 4A). Monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 alpha (MIP-1α), potential stimulators of macrophage proliferation in obese adipose tissue, can lead to adipocyte inflammation[25-26], and we found that IB significantly reduced the secretion of these chemokines (Fig. 4B) and their transcription levels (Figs. 4C, D), as well as the transcription levels of IL-6 (Fig. 4E) and IL-1β (Fig. 4F) induced by TNF-α stimulation in adipocytes. Additionally, cyclooxygenase-2 (COX-2), a common inducible enzyme in the inflammatory response, was also significantly inhibited by IB in terms of its transcription (Fig. 4G) and protein expression levels (Fig. 4H).

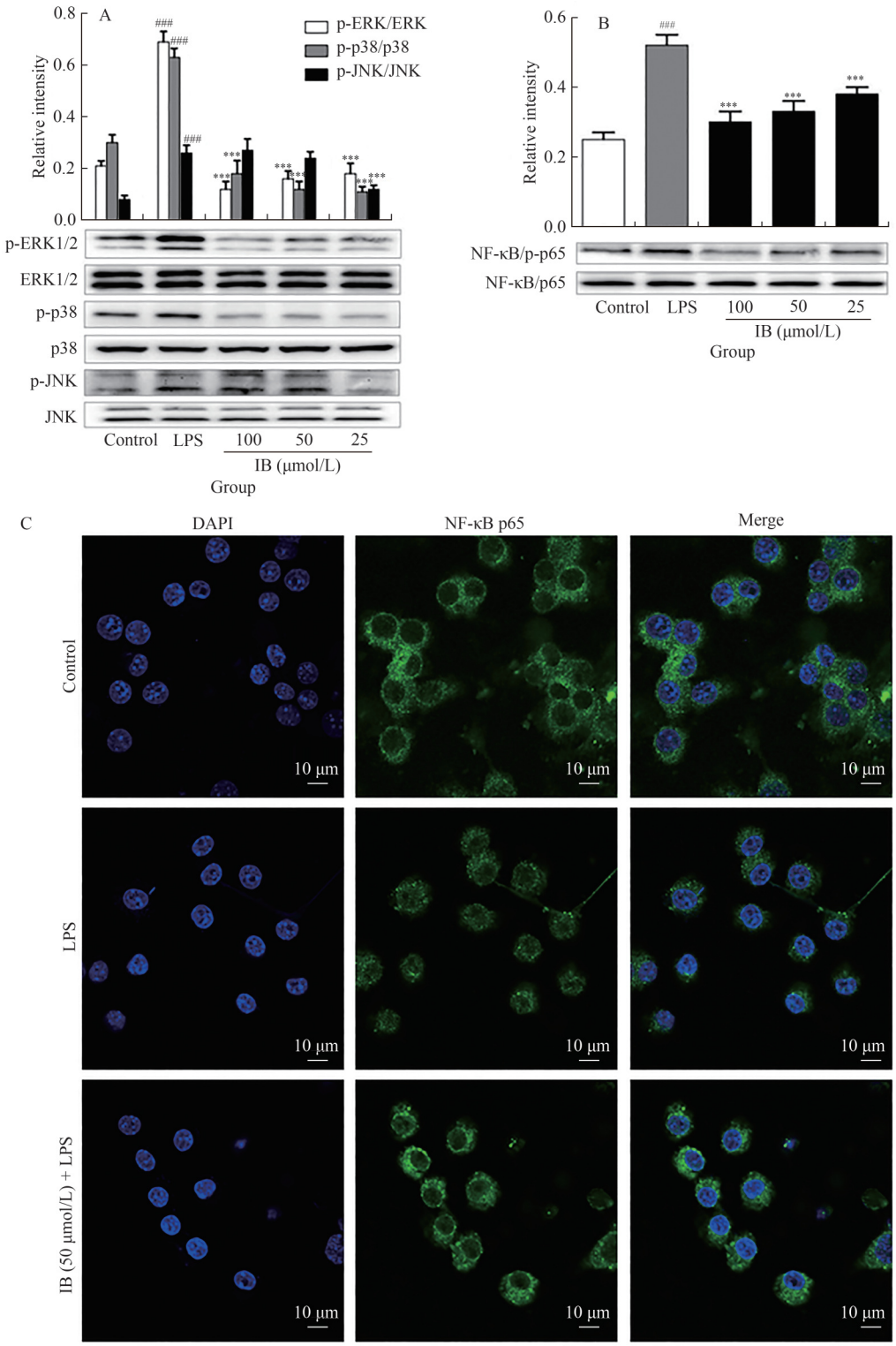


Fig. 3 IB inhibits inflammation in RAW264.7 macrophages via NF-κB and MAPK signaling pathways. (A) The effect of IB on MAPK signaling pathway-related protein expression was analyzed by Western blot and quantified by ImageJ. (B) The effect of IB on the expression of NF-κB signaling pathway-related proteins was analyzed by Western blot and quantified by ImageJ. (C) The effect of IB on p65 nuclear translocation was observed using laser confocal microscopy (scale bar = 10 μm). Data expressed as mean ± SD, $n = 3$. $^{###}P < 0.001$ *vs.* control group; $^{***}P < 0.001$ *vs.* LPS group.

3.5 IB regulates the MAPK/NF-κB signaling pathway in inflammatory 3T3-L1 adipocytes

After determining that IB improves IR caused by inflammation, we sought to further elucidate the mechanism. Using Western blot, we found that IB (25−50 μmol/L) significantly decreased the phosphorylation levels of NF-κB (Fig. 5A), which were elevated by TNF-α stimulation, and likewise reduced JNK phosphorylation levels (Fig. 5B), further confirming the promising anti-inflammatory effects of IB.

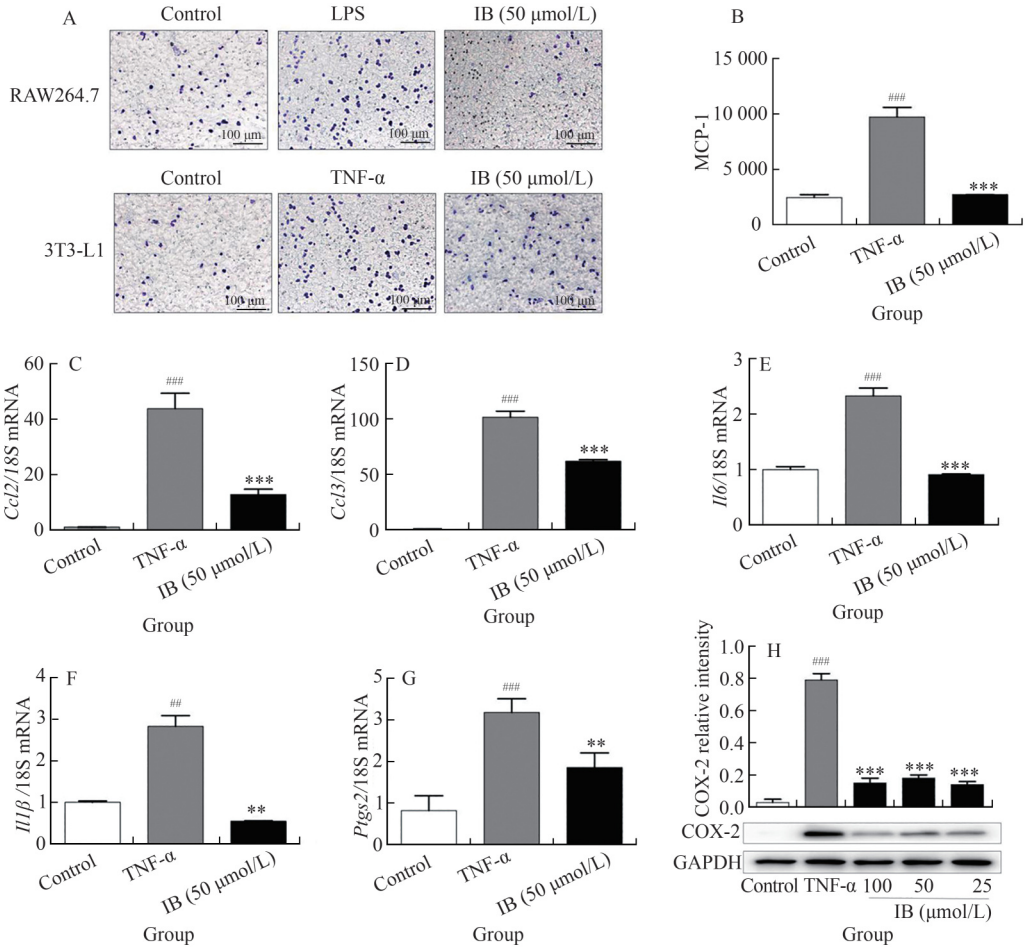


Fig. 4 IB modulates 3T3-L1 adipocytes IR through anti-inflammation. (A) Effect of IB on the migration of RAW264.7 macrophages to 3T3-L1 adipocytes. (B) Effect of IB on the secretion of MCP-1. (C, D) qPCR to detect the effect of IB on *Ccl2* and *Ccl3* expression in 3T3-L1 adipocytes. (E, F) The mRNA expression of *IL-6* and *IL-1β* in 3T3-L1 adipocytes was quantified by qPCR. (G) qPCR to detect the effect of IB on *COX-2* transcription in 3T3-L1 adipocytes. (H) The expression level of COX-2 protein in 3T3-L1 adipocytes was detected by Western blot. Data expressed as mean ± SD, $n = 3$. $^{###}P < 0.001$, $^{##}P < 0.01$ *vs.* control group; $^{***}P < 0.001$, $^{**}P < 0.01$ *vs.* TNF-α group.

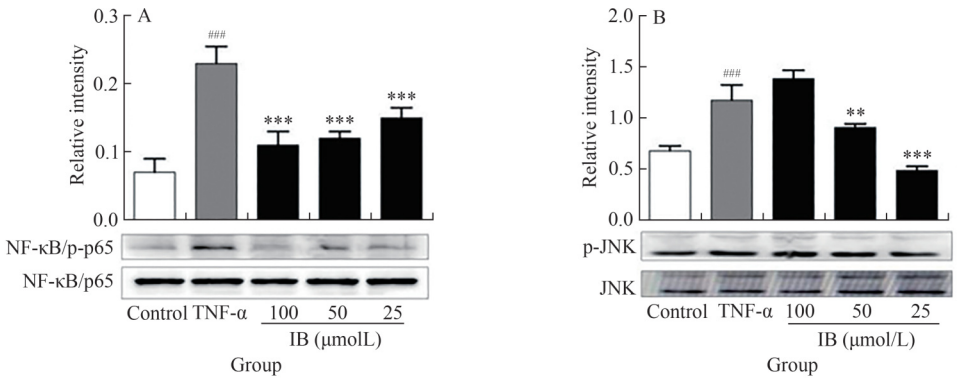


Fig. 5 IB regulates the MAPK/NF-κB signaling pathway in inflammatory 3T3-L1 adipocytes. (A) IB reduces TNF-α-induced NF-κB phosphorylation in 3T3-L1 adipocytes. Densitometry of NF-κB phosphorylation was normalized to NF-κB expression. (B) IB reduces TNF-α-induced JNK phosphorylation in 3T3-L1 adipocytes. Densitometry of JNK phosphorylation was normalized to JNK expression. Data are expressed as mean ± SD, $n = 3$. $^{###}P < 0.001$ *vs.* control group; $^{***}P < 0.001$, $^{**}P < 0.01$ *vs.* TNF-α group.

4. Discussion

Natural products are emerging as a rich source of novel drugs, and the search for substances with hypoglycemic activity in TCM is on the rise[27-30]. IB, a flavonoid obtained from *P. corylifolia*, has been studied for its antibacterial effects[15]. Here, we demonstrate that IB acts as an insulin sensitizer, effectively modulating glucose homeostasis by influencing adipose tissue.

Adipose tissue, functioning as an endocrine organ, secretes various cytokines and adipokines, regulating the inflammatory

response and energy metabolism through autocrine and paracrine mechanisms[31]. However, the balance between inflammatory and anti-inflammatory factors is disrupted in IR, characterized by a low-inflammatory state[32]. Studies indicate a significant correlation between the inflammatory state of IR and T2DM, highlighting the infiltration of macrophages into adipose tissue and the secretion of pro-inflammatory cytokines from adipose tissue[33-34]. Excessive production of chemokines by adipose tissue attracts macrophages, exacerbating the production of pro-inflammatory molecules and accelerating the cycle of inflammation during adipose tissue remodeling. Therefore, we used 3T3-L1 adipocytes and RAW264.7 macrophages as *in vitro* models to investigate the anti-inflammatory and insulin-sensitizing effects of IB. Additionally, these cellular models are frequently employed in previous studies on the development of other hypoglycemic drugs.

Van promotes glucose uptake and utilization by increasing insulin receptor tyrosine kinase activity, enhancing insulin sensitivity and improve IR[35]. We used Van as a positive control drug and found that IB significantly promoted glucose uptake in IR adipocytes at concentrations ranging from 25 to 100 μmol/L, demonstrating superior potency compared to Van. Molecular docking indicated that IB could form hydrogen bonds with the amino acid Arg118 in the insulin receptor, as well as hydrogen bonds with Phe64 and π-π interactions, thereby increasing the interaction between the insulin receptor active site (*α*-CT) and insulin, enhancing insulin signaling. Consequently, we focused our research on the insulin signaling pathway. Previous studies have shown that the PI-3K/Akt insulin signaling pathway is closely related to IR[36-37]. In adipocytes, insulin signaling begins with the activation of insulin receptors and the phosphorylation of substrate tyrosine residues, which in turn activates IRS, with the metabolic effects of insulin relying on IRS protein tyrosine phosphorylation. The absence of IRS-1 or phosphorylated IRS-1 in muscle and adipose tissues is associated with a high risk of diabetes[38-39]. Additionally, phosphorylated IRS binds to the PI-3K regulatory subunit P85, activating its catalytic subunit P110 and thereby activating PI-3K[40]. Akt, a downstream effector and core protein in the PI-3K/Akt insulin signaling pathway, can be activated by PI-3K[41]. We detected the expression of key proteins in the PI-3K/Akt insulin signaling pathway, and through treatment with pathway inhibitors, we found that IB improved IR by activating the PI-3K/Akt insulin signaling pathway and promoting glucose uptake in 3T3-L1 adipocytes.

To mimic the mild inflammatory state associated with systemic IR, we used TNF-α induction in adipocytes to explore the inflammatory mechanism of IB aimed at improving adipocyte inflammation. NF-κB is a major regulator of inflammatory responses in various physiological and pathological processes. In response to stimulation by inflammatory factors[42], NF-κB is activated through phosphorylation of the IKK complex and the subsequent degradation of inhibitor of κ light chain gene enhancer in B cells (IκB)α. The activated NF-κB dimer dissociates from IκBα and is transferred to the nucleus, where it induces the expression of various inflammatory genes[43-44]. We found that IB inhibited LPS-induced P65 activation, prevented NF-κB/P65 translocation from the cytoplasm to the nucleus, and suppressed NF-κB transcriptional activity in macrophages. Another study reported low levels of NF-κB activation in adipose tissue, with activation times similar to those in immune cells, where TNF-α activates the NF-κB signaling pathway, inducing lipolysis, stimulating cytokine expression, and promoting IR production[45]. On the other hand, MAPK, a key class of molecules that receives signals from membrane receptors and transmits them to the nucleus, mediates inflammatory signaling in response to external cellular stimuli, including ERK, p38, and JNK[46]. IB inhibits the expression of phosphorylated proteins ERK, p38, and JNK in LPS-stimulated macrophages, and it can inhibit TNF-α-induced phosphorylated protein expression of JNK in adipocytes. Our data suggest that IB may reduce inflammation in adipose tissue by regulating NF-κB and MAPK signaling pathways to inhibit the inflammatory response of macrophages.

IB exhibits promising medicinal potential, not only as an antimicrobial agent[15], but our results also suggest that IB has the potential to enhance insulin sensitivity. Although we demonstrated that IB can improve inflammation and IR in adipocytes, these studies were conducted in an *in vitro* model with limitations. Our next step will be to study the *in vivo* effects of IB on homeostatic function in adipose tissue and obesity in energy metabolism.

5. Conclusions

Our study elucidates the mechanism by which IB improves inflammation in macrophages and induces IR due to inflammation in fat cells. We found that IB reduces inflammation by inhibiting the NF-κB and MAPK signaling pathways, thereby enhancing insulin sensitivity affected by inflammation. Our findings provide further insight into the conversion of hypoglycemic drugs to IB.

Conflict of interest

Zhenhua Liu is a youth editorial board member, Wenyi Kang and Yan Zhang are associate editors, Bin Cong is the editor-in-chief for *Food Science and Human Wellness* and were not involved in the editorial review on the decision to publish this article. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary information

Supplementary data associated with this article can be found, in the online version, at http://doi.org/10.26599/FSHW.2024.9250369

Reference

[1] G. Dong, S. Adak, G. Spyropoulos, et al., Palmitoylation couples insulin hypersecretion with β cell failure in diabetes, Cell Metab. 35(2) (2023) 332-344. https://doi.org/10.1016/j.cmet.2022.12.012.

[2] Z. Zheng, Y. Xu, W. Liu, et al., Discovery of a potent allosteric activator of DGKQ that ameliorates obesity-induced insulin resistance via the *sn*-1,2-DAG-PKCε signaling axis, Cell Metab. 35(1) (2023) 101-117. https://doi.org/10.1016/j.cmet.2022.11.012.

[3] C. Hamrick, G. Chen, The challenges of future foods from prevention of nutrient deficiencies to the management of diabetes, J. Future Foods 1(1) (2021) 47-57. https://doi.org/10.1016/j.jfutfo.2021.08.001.

[4] L. Wang, B. Wang, N.S. Gasek, et al., Targeting p21Cip1 highly expressing cells in adipose tissue alleviates insulin resistance in obesity, Cell Metab. 34 (1) (2022) 75-89. https://doi.org/10.1016/j.cmet.2021.11.002.

[5] A.R. Cox, P.M. Masschelin, P.K. Saha, et al., The rheumatoid arthritis drug auranofin lowers leptin levels and exerts antidiabetic effects in obese mice, Cell Metab. 34(12) (2022) 1932-1946. https://doi.org/10.1016/j.cmet.2022.09.019.

[6] S. Sriskanthadevan-Pirahas, M.J. Turingan, J.S. Chahal, et al., Adipose mitochondrial metabolism controls body growth by modulating systemic cytokine and insulin signaling, Cell Rep. 39(6) (2022) 110802. https://doi.org/10.1016/j.celrep.2022.110802.

[7] W. Ying, H. Gao, F.C.G. Dos Reis, et al., MiR-690, an exosomal-derived miRNA from M2-polarized macrophages, improves insulin sensitivity in obese mice, Cell Metab. 33(4) (2021) 781-790. https://doi.org/10.1016/j.cmet.2020.12.019.

[8] Y.S. Lee, J. Kim, O. Osborne, et al., Increased adipocyte O_2 consumption triggers HIF-1α, causing inflammation and insulin resistance in obesity, Cell 157(6) (2014) 1339-1352. https://doi.org/10.1016/j.cell.2014.05.012.

[9] H. Xiao, X. Sun, Z. Lin, et al., Gentiopicroside targets PAQR3 to activate the PI3K/AKT signaling pathway and ameliorate disordered glucose and lipid metabolism, Acta Pharm. Sin. B. 12(6) (2022) 2887-2904. https://doi.org/10.1016/j.apsb.2021.12.023.

[10] Z. Xu, D. Liu, D. Liu, et al., Equisetin is an anti-obesity candidate through targeting 11β-HSD1, Acta Pharm. Sin. B. 12(5) (2022) 2358-2373. https://doi.org/10.1016/j.apsb.2022.01.006.

[11] H. Shin, D. Shon, H. Youn, Isobavachalcone suppresses expression of inducible nitric oxide synthase induced by Toll-like receptor agonists, Int. Immunopharmacol. 15(1) (2013) 38-41. https://doi.org/10.1016/j.intimp.2012.11.005.

[12] Y. Dang, S. Ling, J. Duan, et al., Bavachalcone-Induced manganese superoxide dismutase expression through the AMP-activated protein kinase pathway in human endothelial cells, Pharmacology 95(3/4) (2015) 105-110. https://doi.org/10.1159/000375452.

[13] H. Lee, H. Li, M. Noh, et al., Bavachin from *Psoralea corylifolia* improves insulin-dependent glucose uptake through insulin signaling and AMPK activation in 3T3-L1 adipocytes, Int. J. Mol. Sci. 17(4) (2016) 527. https://doi.org/10.3390/ijms17040527.

[14] L. Cao, Y. Wu, K.Y. Liu, et al. *Cornus officinalis* vinegar alters the gut microbiota, regulating lipid droplet changes in nonalcoholic fatty liver disease model mice, Food & Medicine Homology 1 (2024) e9420002. https://doi.org/10.26599/FMH.2024.9420002.

[15] J. Son, A. Kim, S. Oh, et al., Inhibitory effects on *Streptococcus mutans* of antibacterial agents mixed with experimental fluoride varnish, Dent. Mater J. 39(4) (2020) 690-695. https://doi.org/10.4012/dmj.2020-016.

[16] Z. Zhang, Y. Jiang, L. Su, et al., Obesity caused by an OVOL2 mutation reveals dual roles of OVOL2 in promoting thermogenesis and limiting white adipogenesis, Cell Metab. 34(11) (2022) 1860-1874. https://doi.org/10.1016/j.cmet.2022.09.018.

[17] Z. Liu, M. Wang, Y. Liu, et al., Patrinoside and patrinoside A from *Patrinia scabiosaefoli* a improve insulin resistance by inhibiting NF-κB, MAPK pathways and oxidative stress in RAW264.7 and 3 T3-L1 cells, Oxid. Med. Cell Longev. 2023 (2023) 9069645. https://doi.org/10.1155/2023/9069645.

[18] Y. Zhang, P. Lü, J. Ma, et al., *Antrodia cinnamomea* exerts an anti-hepatoma effect by targeting PI3K/AKT-mediated cell cycle progression *in vitro* and *in vivo*, Acta Pharm. Sin. B. 12(2) (2022) 890-906. https://doi.org/10.1016/j.apsb.2021.07.010.

[19] H. Wang, C. Ma, D.X. Sun-Waterhouse, et al., Immunoregulatory polysaccharides from *Apocynum venetum* L. flowers stimulate phagocytosis and cytokine expression via activating the NF-κB/MAPK signaling pathways in RAW264.7 cells, Food Sci. Hum. Well. 11(4) (2022) 806-814. https://doi.org/10.1016/j.fshw.2022.03.012

[20] Y. Wang, B. Tang, L. Long, et al., Improvement of obesity-associated disorders by a small-molecule drug targeting mitochondria of adipose tissue macrophages, Nat. Commun. 12 (2021) 1-16. https://doi.org/10.1038/s41467-020-20315-9.

[21] X. Jiang, J. Wu, Structure and activity study of tripeptide IRW in TNF-α induced insulin resistant skeletal muscle cells, Food Funct. 13(7) (2022) 4061-4068. https://doi.org/10.1039/D1FO02893F.

[22] Y. Yang, W. Zhou, X. Xu, et al., Aprepitant inhibits JNK p38/MAPK to attenuate inflammation and suppresses inflammatory pain, Front. Pharmacol. 12 (2022) 1-13. https://doi.org/10.3389/fphar.2021.811584.

[23] R. Giri, E.C. Hoedt, S. Khushi, et al., Secreted NF-κB suppressive microbial metabolites modulate gut inflammation, Cell Rep. 12 (2022) 1-11. https://doi.org/10.1016/j.celrep.2022.110646.

[24] J.E. Park, E. Kang, J.S. Han, HM-chromanone attenuates TNF-α-mediated inflammation and insulin resistance by controlling JNK activation and NF-κB pathway in 3T3-L1 adipocytes, Eur. J. Pharmacol. 15 (2022) 1-11. https://doi.org/10.1016/j.ejphar.2022.174884.

[25] C. Mazzotta, S. Basu, A.C. Gower, et al., Perivascular adipose tissue inflammation in ischemic heart disease, Arterioscl. Throm. Vas. 41(3) (2021) 1239-1250. https://doi.org/10.1161/ATVBAHA.120.315865.

[26] E. Reda, S. Hassaneen, H.S. El-Abhar, Novel trajectories of bromocriptine antidiabetic action: leptin-IL-6/JAK2/p-STAT3/SOCS3, p-IR/p-AKT/GLUT4, PPAR-γ/adiponectin, Nrf2/PARP-1, and GLP-1, Front. Pharmacol. 9 (2018) 1-13. http://doi.org/10.3389/fphar.2018.00771.

[27] Z. Mao, S. Liu, T. Yu, et al., Yunpi Heluo decoction reduces ectopic deposition of lipids by regulating the SIRT1-FoxO1 autophagy pathway in diabetic rats, Pharm. Biol. 60(1) (2022) 579-588. https://doi.org/10.1080/13880209.2022.2042567.

[28] C. Liu, S. Wang, Z. Xiang, et al., The chemistry and efficacy benefits of polysaccharides from *Atractylodes macrocephala* Koidz, Front. Pharmacol. 13 (2022) 1-13. https://doi.org/10.3389/fphar.2022.952061.

[29] J.S. Li, T. Ji, S.L. Su, et al., Mulberry leaves ameliorate diabetes via regulating metabolic profiling and AGEs/RAGE and p38 MAPK/NF-κB pathway, J. Ethnopharmacol. 283 (2022) 1-13. https://doi.org/10.1016/j.jep.2021.114713.

[30] F.S.A. Saadeldeen, Y. Niu, H. Wang, et al., Regulating glucose metabolism and improving insulin resistance, Food Sci. Hum. Well. 9(3) (2020) 214-228. https://doi.org/10.1016/j.fshw.2020.04.005.

[31] A.M. Cypess, Reassessing human adipose tissue, New Engl. J. Med. 386(8) (2022) 768-779. https://doi.org/10.1056/nejmra2032804.

[32] T.V. Rohm, D.T. Meier, J.M. Olefsky, et al., Inflammation in obesity, diabetes, and related disorders, Immunity 55 (2022) 31-55. https://doi.org/10.1016/j.immuni.2021.12.013.

[33] S. Shen, Q. Liao, Y.K. Wong, et al., The role of melatonin in the treatment of type 2 diabetes mellitus and Alzheimer's disease, Int. J. Biol. Sci. 18(3) (2022) 983-994. https://doi.org/10.7150/ijbs.66871.

[34] X.T. Hao, R. Peng, M. Guan, et al. The food and medicinal homological resources benefiting patients with hyperlipidemia: categories, functional components, and mechanisms, Food & Medicine Homology 1 (2024) e9420003. https://doi.org/10.26599/FMH.2024.9420003.

[35] A. Akhtar, M. Bishnoi, S.P. Sah, Sodium orthovanadate improves learning and memory in intracerebroventricular-streptozotocin rat model of Alzheimer's disease through modulation of brain insulin resistance induced tau pathology, Brain Res. Bull. 164 (2020) 83-97. https://doi.org/10.1016/j.brainresbull.2020.08.001.

[36] Molinaro, B. Becattini, A. Mazzol, et al., Insulin-Driven PI3K-AKT signaling in the hepatocyte is mediated by redundant PI3Kα and PI3Kβ activities and is promoted by RAS, Cell Metab. 29(6) (2019) 1400-1409. https://doi.org/10.1016/j.cmet.2019.03.010.

[37] B.D. Hopkins, C. Pauli, X. Du, et al., Suppression of insulin feedback enhances the efficacy of PI3K inhibitors, Nature 560(7719) (2018) 499-503. https://doi.org/10.1038/s41586-018-0343-4.

[38] D. Liang, W.J. Lin, M. Ren, et al., m6A reader YTHDC1 modulates autophagy by targeting SQSTM1 in diabetic skin, Autophagy 18(6) (2022) 1318-1337. https://doi.org/10.1080/15548627.2021.1974175.

[39] Y. Wu, R. Zhao, M. Li, et al., Novel soybean peptide iglycin ameliorates insulin resistance of high-fat diet fed C57BL/6J mice and differentiated 3T3L1 adipocytes with improvement of insulin signaling and mitochondrial function, Food Sci. Hum. Well. 11(6) (2022) 1565-1572. https://doi.org/10.1016/j.fshw.2022.06.014.

[40] C.P. Hedges, J. Boix, J.K. Jaiswal, et al., Efficacy of providing the PI3K p110α inhibitor BYL719 (Alpelisib) to middle-aged mice in their diet, Biomolecules 11(2) (2021) 150-161. https://doi.org/10.3390/biom11020150.

[41] A.R. Saltiel, Insulin signaling in health and disease, J. Clin. Investig. 131(1) (2021) 142241. https://doi.org/10.1172/jci142241.

[42] Y. Fan, W. Wang, X. Wang, et al., Ganoderma lucidum polysaccharide inhibits LPS-induced inflammatory injury to mammary epithelial cells, J. Future Foods 3(1) (2023) 49-54. https://doi.org/10.1016/j.jfutfo.2022.09.008.

[43] H. Yu, L. Lin, Z. Zhang, et al., Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study, Signal. Transduct. Tar. 5(1)(2020) 209. https://doi.org/10.1038/s41392-020-00312-6.

[44] E. Sun, A. Motolani, L. Campos, et al., The pivotal role of NF-κB in the pathogenesis and therapeutics of Alzheimer's disease, Int. J. Mol. Sci. 23 (16)(2022) 8972. https://doi.org/10.3390/ijms23168972.

[45] N. Akhter, A. Wilson, R. Thomas, et al., ROS/TNF-α crosstalk triggers the expression of IL-8 and MCP-1 in human monocytic THP-1 cells via the NF-κB and ERK1/2 mediated signaling, Int. J. Mol. Sci. 22(19) (2021) 10519. https://doi.org/10.3390/ijms221910519.

[46] Y. Tan, H. Zhou, Y. Lin, et al., FGF2 is overexpressed in asthma and promotes airway inflammation through the FGFR/MAPK/NF-κB pathway in airway epithelial cells, Military Med. Res. 9(1) (2022) 7. https://doi.org/10.1186/s40779-022-00366-3.