

Analysis of Berberine Improving Insulin Resistance in Type 2 Diabetes

Weixuan Chen^{1,*}

¹Department of Anesthesiology,
Changzhi Medical College,
Shanxi046000, China

*Corresponding author:
Chen3580849360@outlook.com

Abstract:

Insulin resistance (IR) is one of the main pathological factors in the development of type 2 diabetes mellitus (T2DM), and improving IR has been an important way to treat T2DM. In recent years, traditional Chinese medicine has gradually begun to be used as a new kind of drug or combined therapy for treating IR. This paper introduces how berberine improves IR from the aspects of pharmacological mechanisms, clinical hypoglycemic data, and future prospects. Berberine has multiple mechanisms of action, mainly by inhibiting the signaling pathways of IR, thereby repairing the normal insulin signaling pathway, promoting glucose uptake by the body, and inhibiting gluconeogenesis. In terms of actual hypoglycaemic effects, berberine alone or in combination with oral hypoglycaemic drugs can significantly reduce the fasting blood glucose, glycosylated haemoglobin and 2-hour postprandial blood glucose levels of patients, and it is safe. However, clinical evidence for berberine is still relatively lacking, and its molecular mechanisms are not fully understood, which can serve as directions for future research. Berberine has the potential to improve insulin resistance in T2DM and has shown good safety and natural alkaloid characteristics providing new ideas for the development of new drugs or combination therapies for diabetes.

Keywords: Insulin resistance; berberine; tumor necrosis factor α ; AMP-activated protein kinase.

1. Introduction

Insulin resistance (IR) has been a severe problem in public health around the world recently, and about 26.53% of adults are affected globally [1]. Based on a large-scale monitoring study of more than 400,000 people in China, it has been found that the triglyceride-glucose index has increased from 8.44 to 8.70,

and the P75 threshold has also risen from 8.83 to 9.10 [2].

IR is the decreased response of the insulin-responsive tissues in the body such as the liver, skeletal muscle and adipose tissue to a high concentration of insulin [3, 4]. The pathological mechanism of IR is complex, involving extensive dysregulation of the insulin signaling cascade [3, 4]. In the face of IR conditions,

there is a reduction in the activation of the insulin receptor, and both the insulin receptor substrate 1/phosphatidylinositol-kinase/protein kinase B (IRS-1/PIK/Akt2) pathway and its downstream pathways are inhibited; as a result, there are various changes in cells and molecules, such as ectopic lipid accumulation, chronic inflammation and endoplasmic reticulum stress [3]. These changes can directly disrupt the homeostatic balance of glucose and lipid metabolism in the body, further reduce tissue sensitivity to insulin, worsen insulin resistance, create a vicious circle, and lead to all kinds of metabolic diseases [3, 4].

At present, the main purpose of clinical treatment for IR is to control blood sugar or alleviate symptoms; Metformin and thiazolidinedione drugs are also often used. The problems of the above strategies are that there is a large number of people, they have a lack of long-term adherence from patients, and there are safety risks such as oedema and weight gain; they are also not suitable for some diseases [5, 6].

Berberine is a plant-derived isoquinoline alkaloid that has been used for a long time and is safe [7, 8]. It is widely distributed and easily obtained; among all sources, *Coptis chinensis* is the most abundant, and it also occurs in the roots, stems, leaves and fruits of plants in the Ranunculaceae, Berberidaceae, and Menispermaceae families [5, 8]. Recently, research has shown that berberine can improve the sensitivity of insulin and decrease fat storage by suppressing the IR-related signalling pathway and activating AMP-activated protein kinase (AMPK) and its downstream signals. It can help to address the current lack of treatment and provide a new idea for personalised intervention in IR [7, 9].

This study highlights three innovative points of berberine in improving IR: first, it regulates both inflammatory and metabolic signaling pathways simultaneously; second, it acts on specific direct targets including MEKK1/MEK/ERK and AMPK α 1; third, it exhibits good safety and synergistic potential with clinical hypoglycemic drugs. Berberine has the potential to improve insulin resistance in T2DM and has shown good safety and natural alkaloid characteristics, providing new ideas for the development of new drugs or combination therapies for diabetes.

2. Molecular and Cellular Basis of Berberine's Improvement in Diabetes

2.1 Inhibition of the MEKK1/MEK/ERK Signaling Pathway

Berberine can correct the impairment of insulin signaling

caused by TNF- α [7]. Li et al. have found that in a model of primary hepatocytes, treatment with TNF- α significantly reduced the activation of a key downstream molecule, Protein Kinase B (Akt), which is stimulated by insulin, and changed the phosphorylation site distribution of Insulin Receptor Substrate-1 (IRS-1)- that is, it promoted the modification of serine sites and suppressed the activation of tyrosine sites. However, Adding 10 μ M of berberine, and the above abnormalities will be reduced to some extent, and the activation status of the corresponding proteins will also return to normal. In addition, the repair process did not change the modification status of the insulin receptor itself; thus, it can be concluded that berberine can repair downstream signaling impairment caused by TNF- α [7].

Berberine selectively inhibits the TNF- α -activated ERK1/2 pathway [7]. Li et al. had conducted numerous studies in biochemistry to demonstrate that berberine can reduce the phosphorylation of ERK1/2 by TNF- α to a certain extent in a concentration-dependent manner. However, berberine did not inhibit the activation of the other main inflammatory regulatory pathway and its key effector proteins that are induced by TNF- α . In addition, the inhibitory effect of TNF- α on the other two branches of the stress response activated by this cytokine, which are also kinases in the same kinase family, did not reach statistical significance. Based on the above results, it can be seen that berberine is highly specific in regulating the downstream pathway of TNF- α , and ERK1/2 is one such target. This is in line with Zhou et al.'s view that berberine can help with T2DM via the MAPK pathway [7, 10].

Further mechanism research has shown that berberine can inhibit the initiation of this cascade reaction by binding to and blocking MEKK1 and MEK1/2; as they are closely related essential kinases, it may fail to activate the MEK/ERK pathway in the first place [7]. Li et al. have studied the effect of berberine on the expression of some genes in the TNF-signaling pathway, and found that when activated, TNF- α forms a complex with MEKK1 to phosphorylate MEK1/2. Experiments have shown that berberine does not alter the expression level of this complex or interfere with its interaction with MEK1/2; however, it can reduce the phosphorylation of MEK1/2 that is triggered by the overexpression of MEKK1. Sequence analysis showed that MEKK1 and MEK1/2 have highly homologous catalytic structures, so berberine can inhibit the activity of MEKK1 by binding to it in the same way and thus block the activation of the MEK/ERK pathway at an upstream level [7].

In addition, berberine can also block downstream signaling by directly interfering with the activity of MEK1/2 [7]. To rule out the indirect effect of other common metabolic

regulation pathways (such as AMPK and PI3K), Li et al. used specific inhibitors, and it was found that the inhibition of ERK1/2 activation by berberine was still there. At the same time, the MEK1/2 inhibitor trametinib can inhibit the TNF- α -induced phosphorylation of ERK1/2 completely and thus have the same effect as berberine. According to molecular docking technology, several stable chemical bonds can be formed between berberine and the catalytic area of MEK1/2. In COS- cells overexpress-

ing MEK1, berberine gradually decreased the phosphorylation of ERK1/2; thus, it was determined that MEK1/2 is a direct target of berberine [7].

In short, berberine can restore IRS-1 tyrosine phosphorylation and Akt activation by inhibiting the abnormal activation of the TNF- α -induced ERK1/2 pathway; that is to say, reduce ERK1/2-mediated IRS-1 serine phosphorylation and target the inhibition of MEKK1 and MEK1/2 activity to repair insulin signaling (Figure1) [7, 10].

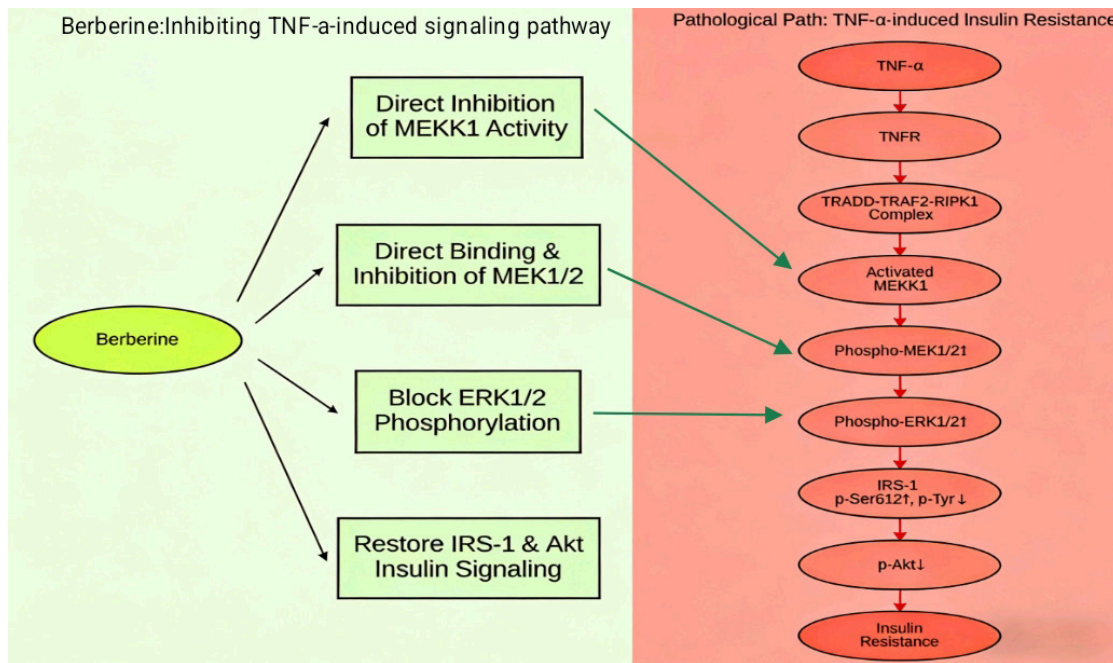


Fig. 1 Berberine selectively blocks the MEKK1/MEK/ERK signaling pathway (Picture: original).

2.1 Activation of AMP-activated protein kinase $\alpha 1$ subunit (AMPK $\alpha 1$) and its downstream signaling pathway

AMPK $\alpha 1$ is the core dependent target of berberine in improving IR [9]. Ren et al. found that berberine can enhance the phosphorylation of some sites on AMPK $\alpha 1$ in wild-type HepG2 cells, but this effect is lost when the gene for AMPK $\alpha 1$ is knocked out in the cells; at the same time, after the knockout of this gene, berberine cannot increase AMPK kinase activity, the basal level of gluconeogenesis rises significantly, and berberine fails to inhibit gluconeogenesis, thus confirming that it is a target of berberine. This result has been supported by Cheng et al., and the review by Askari et al. has also added more evidence to show that AMPK $\alpha 1$ is a target of berberine [11, 12].

Berberine can stimulate AMPK $\alpha 1$ to promote the correction of glucose metabolism disorders [9]. Ren et al. had found that, in wild-type HepG2 cells, a low concentration of berberine can increase the consumption of glucose and

the production of lactate; that is, glucose consumption rose from about 5mmol/L at baseline to 8.5mmol/L, and the corresponding increase in lactate release was about 60 per cent; by promoting the glycolytic pathway, it can improve the efficiency of glucose use and reduce excessive glucose production by the liver through inhibition of gluconeogenesis. However, in the cells where this gene has been knocked out, the above effects do not occur; thus, it can be concluded that berberine regulates glucose metabolism disorders by activating AMPK $\alpha 1$ and reducing blood sugar abnormalities caused by IR. As shown by Askari et al., in their review, one-way berberine can help people with diabetes is by regulating glucose utilization through AMPK [11].

Berberine is an inducer of AMPK $\alpha 1$ in the lipid-metabolism pathway and can reduce fat accumulation [9]. Ren et al. had shown that oleic acid can promote the accumulation of lipids in wild-type HepG2 cells, increase the expression of adipogenic genes, and thus cause lipotoxic

stress. In combination with berberine and oleic acid (OA), it was found that the activity of AMPK α 1 in the cell increased, leading to a reduction in the number of intracellular triglycerides; at the same time, the abnormal up-regulation of adipogenic genes was suppressed and lipid accumulation decreased. After the knockout of the AMPK α 1 gene, the anti-lipid accumulation effect of berberine was gone, and there were no changes in the expression of adipogenic genes; thus, it can be concluded that berberine inhibits fat synthesis and reduces lipotoxicity by suppressing AMPK α 1 to protect the insulin signaling pathway from damage caused by lipid accumulation [9]. Cheng et al. had also found that berberine can decrease the release of inflammatory factors by activating AMPK; thus, AMPK may be one of the reasons why metabolism is impaired in certain conditions [9,11].

Increase the signal of AMPK α 1 and improve insulin sensitivity [9]. Ren et al. have found that berberine can

increase the expression of AMPK-downstream target genes in wild-type HepG2 cells and inhibit lipid synthesis and improve metabolic homeostasis; However, when the gene for AMPK α 1 is knocked out in these cells, berberine is unable to increase the expression of the target genes, suggesting that AMPK α 1 is the upstream regulator of the activation of downstream signaling [9]. The signal transduction pathway can alleviate the suppressive effect of lipid toxicity and metabolic stress on the phosphorylation of insulin receptor substrates, maintain the integrity of the insulin signaling pathway, and thus increase IR [9]. The previous results are in line with what Zhou et al. had concluded in a paper they published, which is that AMPK regulates metabolic signaling pathways [10].

In short, berberine is lipotoxic; that is to say, by reducing the downstream signal, it suppresses fat synthesis and reduces the accumulation of lipids in the body to enhance insulin sensitivity (Figure 2) [9].

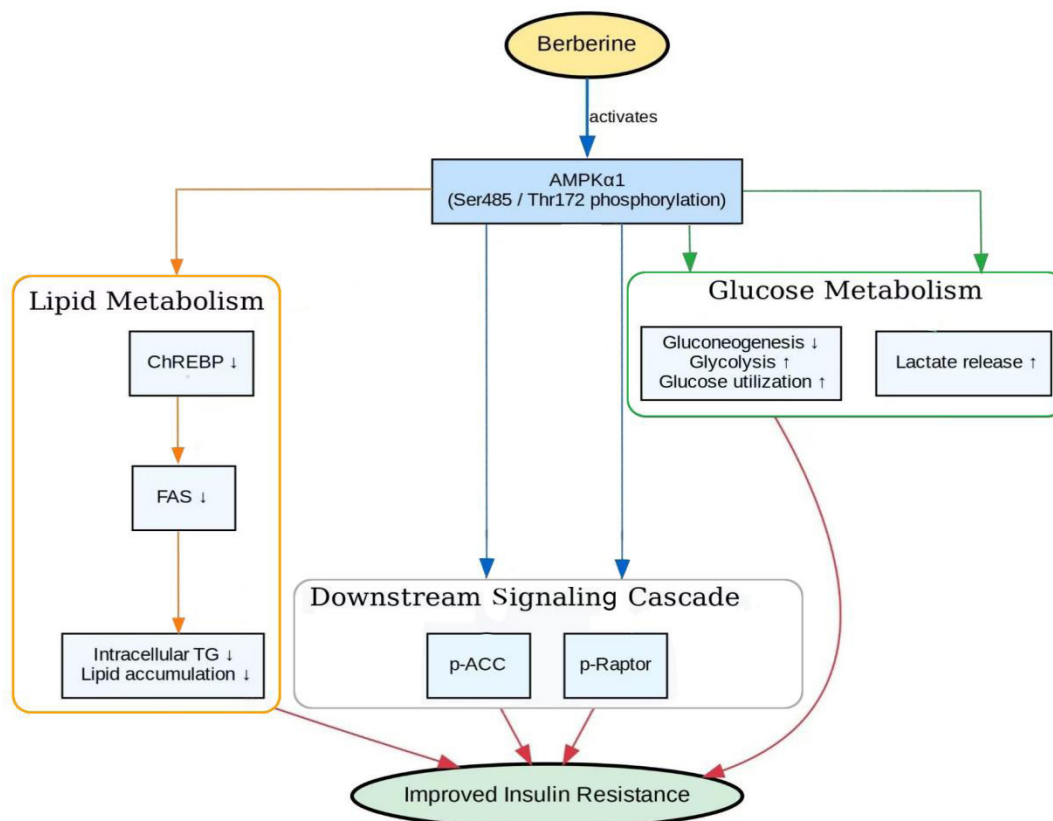


Fig. 2 Berberine activates the AMPK α 1 signaling pathway and its downstream cascades (Picture: original).

3. Clinical Evidence of Berberine in Treating IR

Numerous clinical studies have demonstrated that berberine can improve IR [13, 14]. A systematic review

and meta-analysis by Xie et al., which included 37 randomized controlled trials involving 3,048 patients with T2DM, confirmed that berberine, either as monotherapy or in combination with oral hypoglycemic agents, significantly reduced fasting blood glucose (WMD = -0.82

mmol/L, 95% CI: -0.95 to -0.70), glycated hemoglobin (HbA1c) (WMD = -0.63%, 95% CI: -0.72 to -0.53), and 2-hour postprandial blood glucose (WMD = -1.16 mmol/L, 95% CI: -1.36 to -0.96); the glucose-lowering effect was correlated with baseline blood glucose levels. Regarding safety, the overall incidence of adverse events was lower (RR = 0.73, 95% CI: 0.55 to 0.97), and the risk of hypoglycemia showed no significant difference compared with the control group (RR = 0.483, 95% CI: 0.21 to 1.08) [14]. A study by Wang et al., encompassing 50 randomized controlled trials with 4,150 T2DM patients, found that berberine significantly reduced fasting insulin levels and markedly improved the IR index (SMD = -1.04, 95% CI: -1.81 to -0.28, $P < 0.01$), directly enhancing peripheral insulin sensitivity. After excluding heterogeneous studies, the results remained robust (SMD = -0.70, 95% CI: -1.04 to -0.35, $P < 0.01$), confirming its core glucose-lowering mechanism through the alleviation of IR. Furthermore, this study identified the optimal berberine intervention dosage as 0.9–1.5 g/day, with a treatment duration of 1–3 months, and neither monotherapy nor combination therapy significantly increased adverse reactions [13].

4. Discussion

Despite multiple studies confirming the potential of berberine in improving IR, there are still notable limitations in experimental design and clinical application in the existing evidence. Li et al.'s study revealed the molecular mechanism by which berberine improves IR by inhibiting inflammatory pathways, but its conclusions were mainly based on animal models and in vitro experiments, and its clinical translation value remains questionable [8]. Ren et al.'s study demonstrated that berberine activates the AMPK pathway and regulates key targets of mitochondrial function, but also clearly pointed out its extremely low oral bioavailability (often below 1%). The effective concentrations in in vitro studies often differ in vivo, and there is no unified standard for the optimal hypoglycemic dose [9]. Among strategies to address these deficiencies, combination therapy has shown advantages in synergistic enhancement. Clinical practice has shown that when berberine is used as an adjunctive drug in combination with hypoglycemic agents such as metformin or dapagliflozin, it can further improve IR and glucose-lipid metabolism, with good safety [15]. However, the limitations of berberine itself cannot be ignored. Low bioavailability limits its efficacy as a monotherapy, and although new drug delivery systems have been attempted to overcome this, they often suffer from small sample sizes and short follow-up periods [5]. In addition, the existing human trials on berberine's improvement of IR are limited, and there is a lack

of precise evaluation of pharmacokinetic interactions and the impact of dosing sequence [15]. In summary, future efforts should focus on promoting large-sample, long-term randomized controlled trials to further confirm on clinical evidence that berberine can improve IR.

5. Conclusion

Through a systematic review of existing research, this paper finds that berberine has potential efficacy in improving IR. As a natural is quinoline alkaloid, it can repair the dual regulatory pathway of insulin signaling by regulating inflammation-related pathways and key metabolic kinases. It not only effectively reduces lipotoxic damage and corrects glucose metabolism disorders, but also demonstrates good.

6.Future Prospects

However, at present, there is a lack of data on how much is needed in the body and large-scale clinical studies. In the future, researchers need to increase the scale and duration of randomized controlled trials, explore new drug-delivery systems to overcome the problem of low oral bioavailability, and thus provide more rigorous evidence for the accurate application of berberine in the treatment of metabolic diseases.

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