Berberine Research and Clinical Applications

Research Highlights (see references below)

- ✓ Berberine is a natural alkaloid found in a wide variety of herbs with antimicrobial, anti-inflammatory, and antioxidative effects.
- ✓ Berberine exerts its metabolic and cardioprotective effects by regulating multiple mechanisms involving glucose and insulin metabolism, lipid metabolism, endothelial function, and gut microbiota modulation.
- ✓ The clinical efficacy and safety of berberine has been demonstrated in multiple human clinical trials.

Introduction

Berberine is a naturally occurring compound found in the stem, root, and bark of several plants and herbs, such as Amur cork tree (*Phellodendron amurense*) and Huanglian (*Coptis chinensis* Franch). Berberine has been used in traditional Chinese and Ayurvedic medicine for centuries for the treatment of indigestion, dysentery, and a wide range of infections.[1] In the 1980s, the hypoglycemic effect of berberine was discovered.[2] Since then, a robust amount of research on this alkaloid's pharmacological effects have been elucidated, including its antimicrobial, anti-inflammatory, and antioxidative properties as well as its hypoglycemic action and beneficial effects on lipid metabolism.[1,3]

Mechanisms of action

Berberine exerts its metabolic and cardioprotective effects by regulating multiple molecular targets and pathways. For example:

Glucose and insulin metabolism

- Berberine activates adenosine monophosphate kinase (AMPK), a key regulator in energy metabolism in adipocytes and muscle cells, leading to improved insulin sensitivity, reduced fat accumulation, and energy storage.[4]
- Berberine upregulates the expression of insulin-receptor gene through activation of protein kinase C (PKC) in the liver and muscle cells, leading to improved cellular glucose utilization and reduced insulin resistance.[5]

Lipid metabolism

- Berberine increases the expression of the liver low-density lipoprotein receptor (LDLR) gene by stabilizing its mRNA, which leads to improved clearance of LDL-cholesterol.[6]
- The pro-protein convertase subtilisin/kexin type 9 (PCSK9) downregulates LDLR by promoting degradation of LDLR. Berberine decreases PCSK9 mRNA and protein levels, thereby blocking the PCSK9-mediated LDLR degradation.[7]

Endothelial function

- High oxidative stress and low nitric oxide production due to dysregulated glucose, lipid metabolism, and proinflammatory factors contribute to endothelial dysfunction.[8] Via activation of AMPK, berberine increases endothelial nitric oxide synthase (eNOS) expression and suppresses oxidative stress.[9]
- Berberine reduces oxidized LDL (oxLDL)-stimulated production of reactive oxygen species and monocyte adhesion to endothelial cells via suppression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1).[10]

Gut microbiota modulation

- Berberine increases the amount of gut bacteria that produce short-chain fatty acids (SCFAs). Increased levels of SCFAs contribute to numerous benefits for the host.[11,12]
- Berberine increases abundance of *Akkermansia* spp. (which regulates inflammation and gut barrier integrity) and decreases endotoxemia as well as reduces intestinal and arterial proinflammatory mediators in mice fed a high-fat diet.[13]

Clinical Applications at a Glance

The health benefits of berberine have been studied in many different areas. Key human clinical studies involving berberine are summarized below.

Health Condition (Sample Size)	Study Design; Berberine Dosage	Main Findings
T2D (n=36)[14]	Pilot trial; 500 mg t.i.d. or metformin (500 mg t.i.d.) for 3 mo	• The hypoglycemic effect (reduction in HbA1c, fasting blood glucose, postprandial blood glucose and plasma TG) of berberine was similar to that of metformin
T2D and dyslipidemia (n=116)[15]	DB RCT; 500 mg b.i.d. or placebo for 3 mo	• Significant reductions in fasting plasma glucose, postprandial plasma glucose, HbA1c, TG, total cholesterol, and HDL-C vs. placebo
T2D (n=97)[16]	RCT; 1,000 mg/d or metformin (1.5 g/d) or rosiglitazone (4 mg/d) for 2 mo	• Reductions in fasting blood glucose, HbA1c, and TG vs. baseline • Hypoglycemic effects similar to those of metformin and rosiglitazone
T2D (n=2,313)[17]	Review of 28 clinical trials; 300-3,000 mg/d (majority 900-1,800 mg/d) for 14-730 d (majority 30-90 d); control groups varied (lifestyle, metformin, simvastatin, sulfonylurea, or placebo)	• Pooled results showed reductions in fasting blood glucose, postprandial blood glucose, and HbA1c vs. control
Hypercholesterolemia but low CV risk (n=144)[18]	DB RCT; after 6 mo diet (600 kcal daily deficit) and exercise (20-30 min, 3-4 times/wk), 500 mg b.i.d. or placebo for 3 mo; after a 2-mo washout period, 500 mg b.i.d. or placebo for additional 3 mo	• 6 mo run-in reduced body weight and BMI as expected • The first 3 mo berberine reduced total cholesterol and LDL-C vs. placebo • Lipids worsened during washout period as expected • Resumed berberine for 3 mo reduced total cholesterol, LDL-C, and TG and increased HDL-C vs. placebo
Hyperlipidemia (n=874)[19]	Review of 11 RCTs; 900-1,500 mg/d for 8-52 wk (majority 8-12 wk); control groups varied (lifestyle, metformin, simvastatin, sulfonylurea, or placebo)	• Pooled results showed reductions in total cholesterol, TG, and LDL-C and increases in HDL-C vs. control
Dyslipidemia (n=2,147)[20]	Meta-analysis of 16 RCTs	• Pooled results showed reductions in total cholesterol, LDL-C, and TG and increases in HDL-C vs. control
Metabolic syndrome (n=80)[21]	Clinical trial; receiving 4 tablets (dose not available) t.i.d. or regular therapy for 1 mo	• Reductions in fasting blood glucose, postprandial blood glucose, insulin resistance index, and blood lipid indexes vs. regular therapy • Reductions in the inflammatory markers, hs-CRP, IL-6, and TNF-α vs. regular therapy
PCOS and insulin resistance (n=89)[22]	RCT; all received cyproterone acetate, then randomly assigned to 500 mg t.i.d. or metformin 500 mg t.i.d., or placebo for 3 mo	• Reductions in WC, WHR, total cholesterol, TG, and LDL-C, and increases in HDL-C and SHBG vs. metformin • Reductions in WHR, fasting blood glucose, fasting insulin, HOMA-IR, total cholesterol, LDL-C, and TG and increases in HDL-C and SHBG vs. placebo
PCOS undergoing IVF treatment (n=150)[23]	RCT; 500 mg t.i.d. or metformin 500 mg t.i.d. or placebo for 3 mo before ovarian stimulation	• Reductions in total testosterone, free androgen index, fasting glucose, fasting insulin, and HOMA-IR and increases in SHBG vs. placebo • Treatment before the IVF cycle increased the pregnancy rate and reduced the incidence of severe ovarian hyperstimulation syndrome
PCOS and insulin resistance (n=735)[24]	Meta-analysis of 9 RCTs; 900-1,500 mg/d or metformin 500-1,500 mg/d or cyproterone 1 tablet/d for 3 mo	• Effects on BMI, HOMA-IR, total cholesterol, TG, and LDL-C similar to those of metformin • Combination of berberine with cyproterone was more effective than cyproterone alone in reducing WHR, HOMA-IR, total cholesterol, TG, and LDL-C and increasing HDL-C
NAFLD (n=501)[25]	Meta-analysis of 6 RCTs; 300-500 mg t.i.d. for 12-16 wk	• Reductions in total cholesterol, LDL-C, HbA1c, postprandial glucose, and ALT vs. control
Acute coronary syndrome following PCI (n=130)[26]	Clinical trial; receiving 300 mg t.i.d. plus standard therapy or standard therapy alone for 1 mo	• Reductions in the inflammatory markers, MMP-9, ICAM-1, and VCAM-1 vs. standard therapy
IBS-D (n=196)[27]	RCT; 400 mg/d or placebo for 8 wk followed by a 4-wk washout	• Reduction of diarrhea frequency, abdominal pain frequency, and urgent need for defecation frequency vs. placebo

ALT= alanine transaminase; **BMI=** body mass index; **CV=** cardiovascular; **d=** day(s); **DB=** double-blind; **HbA1c=** hemoglobin A1c; **HDL-C=** high-density lipoprotein cholesterol; **hs-CRP=** high-sensitivity C-reactive protein; **HOMA-IR=** homeostatic model assessment of insulin resistance; **ICAM-1=** intercellular adhesion molecule-1; **IL-6=** interleukin-6; **IBS-D=** diarrhea predominant irritable bowel syndrome; **IVF=** *in vitro* fertilization; **LDL-C=** low-density lipoprotein cholesterol; **MMP-9=** matrix metalloproteinase-9; **mo=** month(s); **NAFLD=** nonalcoholic fatty liver disease; **PCI=** percutaneous coronary intervention; **PCOS=** polycystic ovary syndrome; **RCT=** randomized controlled trial; **SHBG=** sex hormone-binding globulin; **T2D=** type 2 diabetes; **TG=** triglycerides; **TNF-α=** tumor necrosis factor-α; **VCAM-1=** vascular cell adhesion molecule-1; **WC=** waist circumference; **WHR=** waist-to-hip ratio; **wk=** week(s)

Safety

- The safety of berberine has been demonstrated in multiple meta-analyses involving subjects with dyslipidemia, hyperlipidemia, or type 2 diabetes; no severe adverse events associated with berberine were reported.[19,20,28]
- In a meta-analysis involving women with polycystic ovary syndrome and insulin resistance, the adverse event profile of berberine is less severe than that of metformin.[24]
- The main complaints associated with berberine consumption were gastrointestinal, such as diarrhea, constipation, and flatulence.[14,19]

Potential drug interactions

- Two weeks of berberine administration (300 mg t.i.d.) decreased cytochrome P450 (CYP)2D6, CYP2C9, and CYP3A4 activities in 17 healthy male subjects, although variability among subjects was relatively large.[29]
- Combined administration of berberine (300 mg/d) with simvastatin (40 mg/d) or with fenofibrate (200 mg/d) for seven days did not result in clinically obvious pharmacokinetic interactions.[30]
- Potential interaction between berberine and metformin has not been studied in humans, although metformin is not metabolized by CYP enzymes and is excreted unchanged in the urine.[31]
- One study found berberine increased bioavailability of P-glycoprotein substrates digoxin and cyclosporine in rats.[32] However, the effect of berberine on P-glycoprotein expression/activity depends on the cell line studied.[33] Therefore, potential interactions between berberine and P-glycoprotein substrates in humans remain to be studied.

References

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