Berberine SAP

*Science-based berberine for optimal metabolic function**

Berberine is an active constituent found in a variety of species of plants. Newer studies have found berberine has biological effects in several pathways in the body, indicating it may be a potential treatment for metabolic syndrome.[1]* Metabolic syndrome is hypothesized as beginning with an accumulation of lipids in nonadipose tissues, known as nonalcoholic fatty liver disease (NAFLD).[1] Berberine also has studies supporting its ability to reduce symptoms associated with NAFLD, as well as showing significant antidiabetic effects and lipid-lowering capability.[2][3][4]* Historically, berberine has been used for its antimicrobial activity, as berberine is active against a wide range of organisms including bacteria, viruses, fungi, helminths and chlamydia.[1]*

SUPPLEMENT FACTS

Serving Size: 1 Capsule

	Amount Per Serving	% Daily Value
Berberine (*Berberis aristata*) (from 300 mg of berberine hydrochloride)	271.5 mg	**

**Daily Value not established

This product is non-GMO and vegan friendly.

Contains no: Gluten, soy, wheat, corn, eggs, dairy, yeast, citrus, preservatives, artificial flavor or color, starch, or sugar.

Berberine SAP contains 90 capsules per bottle.

DIRECTIONS FOR USE

Adults: Take 1 capsule three times daily or as directed by your healthcare practitioner. Consult a healthcare practitioner for use beyond 3 months.

INDICATIONS

Berberine SAP can help:

- Reduce nonalcoholic fatty liver disease (NAFLD).*
- Regulate symptoms associated with metabolic syndrome.*
- Support healthy cholesterol and glucose levels in patients with type 2 diabetes or hypercholesterolemia.*
- Promote healthy microbial activity against bacteria, viruses, helminths, and fungi, without having a negative impact on beneficial bacteria.*

CAUTIONS AND WARNINGS

Consult a healthcare practitioner prior to use if you have a kidney disorder; if you have blood pressure problems; if you have hypoglycemia or hypotension; if you have gall stones; if you have diabetes; if you have a liver disorder; if you have a cardiovascular disease; if you have blood disorders or leucopenia; or if you are taking prescription medications, as berberine may alter their effectiveness. Some people may experience skin irritation, facial flushing, and slowed heart rate.

Contraindication: Do not use if you are pregnant or breastfeeding.

Known adverse reactions: May cause gastrointestinal discomfort such as constipation, vomiting, abdominal pain, or diarrhea; in which case, discontinue use and consult a healthcare practitioner.

Do not use if seal is broken. Keep out of reach of children.

PURITY, CLEANLINESS, AND STABILITY

All ingredients listed for each **Berberine SAP** lot number have been tested by an ISO 17025–accredited third-party laboratory for identity, potency, and purity.

*** These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

Scientific Advisory Panel (SAP): adding nutraceutical research to achieve optimum health

NFH®

351, Rue Joseph-Carrier, Vaudreuil-Dorion, Quebec, J7V 5V5
T 1 866 510 3123 • F 1 866 510 3130 • nfh.ca

For healthcare professional use only.

Berberine is an isoquinoline alkaloid present in a variety of plant species including *Hydrastis canadensis, Coptis chinensis, Berberis aquifolium,* and *Berberis vulgaris.*[1] Historically, berberine is well-known for its use as an antimicrobial; however, more recent research has demonstrated that this alkaloid has a multitude of therapeutic applications, including metabolic diseases like obesity, metabolic syndrome, and type 2 diabetes.[1]

BERBERINE METABOLISM

Berberine metabolites become widely distributed within the body, with kinetic studies showing berberine is found in the liver, kidneys, spleen, lung, and brain. It is found in its highest concentration in the liver at about a 70-fold increase versus plasma.[1]

BERBERINE AND CHOLESTEROL

Berberine has been reported to inhibit both triglyceride and cholesterol synthesis in human hepatoma cells, as well as from primary hepatocytes.[1] Multiple animal studies have demonstrated that berberine can alleviate hyperlipidemia and fatty liver in obese and obese and diabetic rats.[2] In another study, mice consumed a high-fat diet to induce fatty liver, and after sixteen weeks of berberine supplementation there was a 14% reduction in liver lipid content as well as an alleviation of hepatic stenosis.[1]

Human clinical investigations have shown that berberine supplementation may reduce aspartate and alanine transaminase levels in patients with type 2 diabetes, indicating that berberine may improve liver function.[1] Berberine has also been shown to reduce liver necrosis in both steatosis due to hepatitis C infection as well as non-alcoholic steatosis.[1] Another study demonstrated berberine's positive effect on its ability to lower hypercholesterolemia, specifically LDL-C, in elderly hypercholesterolemic patients who were statin-intolerant.[1]

BERBERINE AND INSULIN

Berberine has been shown to regulate glucose metabolism both in vitro and in vivo.[3] In a pilot study comparing the efficacy of berberine versus metformin in newly diagnosed type 2 diabetic patients, researchers demonstrated that after 3 months, the hypoglycemic effect of berberine (500 mg three times per day) was similar to metformin.[3] Clinical effects in the berberine group included statistically significant decreases in fasting blood glucose, postprandial blood glucose, hemoglobin A_{1c} (HbA_{1c}) and plasma triglycerides.[3] In a follow-up study of adults with poorly controlled type 2 diabetes, patients were administered berberine for 3 months.[3] Berberine was able to lower fasting blood glucose and postprandial blood glucose from week 1 through to the end of the trial. In addition, statistically significant decreases in HbA_{1c} and fasting plasma insulin as well as in total cholesterol and low-density lipoprotein cholesterol were observed.[3] During the trial, 34.5% of patients experienced transient gastrointestinal adverse effects; however, functional liver or kidney damages were not observed in any patients.[3] When berberine dosages were reduced to 300 mg three times per day, gastrointestinal symptoms improved significantly.[3] Researchers concluded that berberine is a potent oral hypoglycemic agent with beneficial effects on lipid metabolism.[3]

Berberine may impact insulin levels by upregulating insulin receptor expression. In patients treated with berberine, researchers found a significant elevation in the percentage of peripheral blood lymphocytes that express insulin receptors.[4] Berberine was also effective at lowering fasting blood glucose in patients with chronic hepatitis B or C and type 2 diabetes, with patients also demonstrating improvement in liver function observed via a reduction in liver enzymes.[4]

Berberine has the ability to stimulate insulin secretion in pancreatic islet cells as well as HIT-T15 cells, which may also play a role in its anti-diabetic activity. When Hep G2 cells produce interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), this results in a state of inflammation which in turn impairs the insulin pathways. Berberine treatment inhibits the production of both IL-6 and TNF-α, associated with an improvement in the insulin-signaling cascade. Therefore, berberine may have its effect on enhancing insulin secretion through its anti-inflammatory activity.[1] Berberine may also promote activation of messenger RNA transcription of the insulin receptor, contributing to berberine's ability to regulate insulin sensitivity.[1]

BERBERINE AS AN ANTIMICROBIAL

Berberine has been shown to have significant antimicrobial activity against bacteria, fungi, parasites, helminths, and viruses.[1] Berberine has considerable data against several bacteria including *Streptococcus, Salmonella, Klebsiella, Clostridium, Pseudomonas, Proteus, Shigella, Vibrio,* and *Cryptococcus* species, as well as being effective in treating *Escherichia coli* diarrhea.[1] Data also shows that berberine exerts this positive effect without harming indigenous *lactobacilli* and *bifidobacteria* in the intestinal system.[1]

Berberine has also been researched as a treatment for multidrug-resistant *E. coli*.[5] Five multidrug-resistant (MDR) STEC/EPEC and five MDR ETEC isolates from yaks with hemorrhagic diarrhoea were selected for the study.[5] Antibacterial activity of berberine was evaluated, and researchers concluded that berberine may be a good antibacterial treatment against MDR *E. coli*.[5]

BERBERINE AND GUT FLORA

A study exploring the role of berberine's effect on endotoxemia in mice found that pretreating cells with berberine protected the endothelial tight junctions against disruption which could potentially have a similar effect on human Caco-2 cells.[1] Therefore, berberine treatment may block endotoxemia from entering into circulation, and thus reduce hepatic inflammation and progression of NAFLD.

Researchers have also hypothesized that part of berberine's beneficial effect in patients with diabetes mellitus is due to its ability to modulate gut flora.[6] Recent evidence suggests that gut flora composition may be associated with obesity and type 2 diabetes, both ailments associated with low-grade inflammation.[6] Since berberine is poorly absorbed, it acts topically in the gastrointestinal system and is able to inhibit bacterial cell division which may play a role in regulating gut flora.[6]

REFERENCES

1. Liu, Y., et al. "Update on berberine in nonalcoholic Fatty liver disease." *Evidence-Based Complementary and Alternative Medicine* Vol. 2013 (2013): 308134.
2. Kim, W.S., et al. "Berberine improves lipid dysregulation in obesity by controlling central and peripheral AMPK activity." *American Journal of Physiology* Vol. 296, No. 4 (2009): E812–E819.
3. Yin, J., H. Xing, and J. Ye. "Efficacy of berberine in patients with type 2 diabetes mellitus." *Metabolism* Vol. 57, No. 5 (2008): 712–717.
4. Zhang, H., et al. "Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression." *Metabolism* Vol. 59, No. 2 (2010): 285–292.
5. Bandyopadhyay, S., et al. "Potential antibacterial activity of berberine against multi drug resistant enterovirulent *Escherichia coli* isolated from yaks (*Poephagus grunniens*) with haemorrhagic diarrhoea." *Asian Pacific Journal of Tropical Medicine* Vol. 6, No. 4 (2013): 315–319.
6. Han, J., H. Lin, and W. Huang. "Modulating gut microbiota as an anti-diabetic mechanism of berberine." *Medical Science Monitor* Vol. 17, No. 7 (2011): RA164–RA167.

Berberine SAP

*Science-based berberine for optimal metabolic function**

INDICATION SPECIFIC DOSAGE SUMMARY BASED ON HUMAN CLINICAL RESEARCH#

#Please note these suggestions are guidelines based on the clinical studies. Evidence for efficacy and safety has been qualitatively (study quality in terms of study design, sample size, appropriate methods of analysis, use of appropriate placebo/control, bias etc) assessed and has been rated using a 5 star ★ rating classification.

Indication	Suggested dosage	Supporting evidence and study outcomes	Study design	Outcome measures/ selection criteria for studies	Safety	Evidence quality rating
Women's Health						
PCOS[1,2,3]	3 capsules/day	Significant improvement in clinical, hormonal, and lipid parameters in the berberine group compared to the metformin and myoinositol group ($p<0.0001$)	Randomized, prospective study. (n=136, 12 weeks); 1000 mg of berberine hydrochloride/ day or 1000 mg of metformin hydrochloride/day or 2000 mg of myoinositol/day	Mean weight, waist circumference (WC), waist-hip ratio (WHR), body mass index, carbohydrate metabolic parameters, fasting blood glucose (FBS), serum fasting insulin (FI), serum total cholesterol (TC), triglycerides (TG), LDL-C, and serum HDL-C levels	No severe adverse effects reported	★★★
	5 capsules/day	Significant improvement in the metabolic and hormonal derangements of the women in the berberine group, especially in the obesity and dyslipidemia-related parameters, waist-hip ratio ($p<0.01$), TC, TG, and LDL-C levels ($p<0.05$)	Randomized placebo-controlled study. (n=89, 3 months); 1500 mg of berberine hydrochloride/day + cyproterone acetate (CPA) 35 mg (ethinyl estradiol and 2.0 mg CPA) or 1500 mg of metformin/ day + CPA	Body mass index (BMI), WHR, fasting plasma glucose (FPG) and insulin (FIN), TC, TG, (HDLC), and LDLC	No severe adverse effects reported	★★★★
	3 to 6 capsules/day	Berberine significantly improved insulin resistance and dyslipidemia and also showed a significant decrease in decreasing androgen levels and LH/ FSH ratio	12 randomized, controlled studies. (n=1544, 3 to 24 weeks); 900, 1500 or 2000 mg of berberine/day	Live birth rate, clinical reproductive outcomes, reproductive hormone levels, glucose and lipid profiles, BMI, WC, and WHR	No severe adverse effects reported. Gastrointestinal adverse effects reported in the berberine group in 3 randomized, controlled studies	★★★★
Fertility[4]	5 capsules/day	Significant decrease in BMI, waist circumference, and waist/hip ratio in the berberine group	Randomized, prospective, placebo-controlled, double-blind study. (n=128, 3 months); 1500 mg of berberine hydrochloride/day or 1500 mg of metformin/day	BMI, waist circumference and waist/hip ratio, total testosterone, and free androgen index, (FAI), the difference in ovarian stimulation and the thickness of uterine endometrium	No severe adverse effects reported. One of the berberine group participants had transient gastrointestinal side effects, including diarrhea	★★★
Cardiovascular and Metabolic Health						
Cardiovascular health[5,6,7,8,9,10]	2 to 5 capsules/day	After berberine consumption, there is a significant reduction in total cholesterol, triglycerides, and LDL-C levels. An overall beneficial effect of berberine on hyperlipidemia was reported	11 randomized, controlled studies. (n=874, 8 to 52 weeks); 600 to 1500 mg of berberine/day	Anti-dyslipidemic and hypoglycemic effects, blood lipids, and glucose levels	No severe adverse effects reported. Mild to moderate constipation was reported in the berberine group in four RCTs	★★★★
	2 to 5 capsules/day	Significant reduction of TC, LDL-C, TG, and HDL-C levels after berberine consumption with a statistical significance of $p<0.00001$, $p<0.00001$, $p=0.002$ and $p=0.001$ respectively	16 randomized, controlled studies. (n=2147, 1 to 24 months); 600 to 1500 mg of berberine/day	Lipid profile parameters including TC, LDL-C, TG, and HDL-C	No severe adverse effects reported	★★★★
	3 to 6 capsules/ day for improving TG, TC, and weight, 6 capsules/day for insulin and HOMA-IR	Significant reduction of triglyceride and total cholesterol, LDL, fasting blood glucose, systolic blood pressure, and weight with a statistical significance of $p<0.001$ The optimal dose of berberine was suggested to be 1 g/day for TG, TC, and weight, 1.8 g/ day for insulin and HOMA-IR, and 5 g/ day for HDL.	49 randomized, controlled studies. (n=1426, 4 to 104 weeks); 900-1800 mg/day	TG, TC, LDL, HDL, insulin, HbA1c, homeostasis model assessment-insulin resistance (HOMA-IR), systolic blood pressure (SBP), diastolic blood pressure (DBP), C-reactive protein (CRP), interleukin-6, (IL-6)	No severe adverse effects reported; Mild to moderate gastrointestinal adverse effects, including nausea, constipation and diarrhea were reported in some studies.	★★★★
	1 to 3 capsules/day	The berberine group significantly reduced LDL and total cholesterol ($p<0.05$).	11 randomized, controlled studies. (n=1386, 1 month to 2 years); 300 to 1000 mg of berberine/day	TG, TC, LDL-C, HDL-C	No severe adverse effects reported. Constipation was observed in the berberine group	★★★

	4 capsules/day	Significant reduction in the POAF incidence, lipopolysaccharide, CRP (C-reactive protein), and IL (interleukin)-6 levels after berberine treatment.	Randomized, double-blind, placebo-controlled study. (n=200, 7 days); 1200 mg of berberine/day	Postoperative atrial fibrillation (POAF), POAF burden, intestinal endotoxin, and serum inflammatory biomarker levels	No severe adverse effects reported	★★★
	3 capsules/day	Significant reduction in total cholesterol, LDL, and HDL levels after berberine treatment	Randomized, double-blind, placebo-controlled, parallel study, (n=84, 12 weeks); 1000 mg of berberine/day	LDL-C, TC, TG, HDL-C, thromboxane A2, systolic and diastolic blood pressure, and serum testosterone	No severe adverse effects reported	★★★★
Diabetes[11,12,13,14]	5 capsules/day	Significant decrease in fasting blood glucose, postprandial blood glucose, plasma triglycerides, HbA1C, fasting plasma insulin, and HOMA-IR levels after berberine treatment	Randomized pilot studies. (Study 1: n=36, 3 months; Study 2: n=48, 3 months); 1500 mg of berberine/day or 1500 mg of metformin	Blood glucose, serum insulin, Plasma TG, TC, HDL-C, LDL-C, alanine transaminase (ALT), γ glutamyl transpeptidase (γ-GT), creatinine concentrations, and HOMA-IR	No severe adverse effects reported. Diarrhea, constipation, flatulence, and abdominal pain were reported in the combined treatment	★★★
	4 capsules/day	Significant changes in glycated hemoglobin were noticed in both berberine alone and the berberine + probiotics group ($P < 0.001$). *Ruminococcus bromii* is also observed to mediate the inhibition of deoxycholic acid along with berberine	Randomized, double-blind, placebo-controlled study. (n=409, 12 weeks); 1200 mg of berberine (± probiotics)/day ≥50 billion CFU (nine proprietary strains of lactic acid bacteria)	HbA1c, serum insulin, C peptide, fasting plasma glucose, post-load plasma glucose (PPG), TGs, TC, and LDL-C levels	No severe adverse effects reported. Gastrointestinal side effects were reported in the berberine group	★★★
	3 capsules/day	Significant improvement in fasting glucose plasma levels and postprandial plasma glucose in the berberine group	Randomized, parallel-controlled, multi-center, double-blind study. (n=300, 16 weeks); 1000 mg of berberine/day + probiotics (10^8 *Bifidobacterium adolescentis*)	HbA1c, blood pressure; TC, LDL-C, HDL-C, TG, body weight (BW), BMI, HOMA index, insulin early-phase and late-phase secretion index; intestinal glucagon-like peptide-1 (GLP-1), and gut microbiota	No severe adverse effects reported	★★★
	3 capsules/day	Significant reduction in fasting blood glucose, hemoglobin A1c, triglyceride, and insulin levels in the berberine group; also, enhanced liver function was observed	Randomized study. (n=50, 2 months); 1000 mg of berberine hydrochloride/day or 1500 mg of metformin/day	Fasting blood glucose, HbA1c, TG, serum insulin levels, liver and kidney function	No severe adverse effects reported	★★★

Gastrointestinal Health

Gastrointestinal health[15]	3 capsules/day	Significant effects on the eradication of *H. pylori* were noticed in the berberine group	Randomized, open-label, non-inferiority, phase IV study. (n=612, 14 days); 1000 mg of berberine/day plus 1 esomeprazole tablet, 2 amoxicillin capsules, 1 clarithromycin tablet	Eradication of *H. pylori*	No severe adverse effects reported. Gastrointestinal symptoms and bitter taste were observed in the berberine group	★★★★

Immunity

Leukocyte-mediated killing of endothelial cells[16,17]	3 capsules/day	Significant inhibition of the diabetes-induced increase in the leukocyte-mediated killing of human retinal endothelial cells (HRECs) after berberine treatment	Single-center study. (n=28, 1 month); 1000 mg of berberine/day	Analysis of leukocyte-mediated killing of endothelial cells	No severe adverse effects reported	★★★
	3 capsules/day	Significant improvement in PANSS level and decrease in plasma CRP level in the berberine group. Significant anti-inflammatory effects were also observed	Randomized, double-blind, placebo-controlled study. (n=59, 8 weeks); 900 mg of berberine/day	Positive and Negative Syndrome Scale (PANSS), inflammatory markers (serum IL-1β, serum IL-6, serum TNF-α, plasma CRP)	No severe adverse effects reported	★★★

References:

1. Mishra N., et al. "Study on the Effect of Berberine, Myoinositol, and Metformin in Women with Polycystic Ovary Syndrome: A Prospective Randomised Study." *Cureus*. No. 1 (2022 Jan 31): 14-e21781.
2. Wei W., et al. "A clinical study on the short-term effect of berberine in comparison to metformin on the metabolic characteristics of women with polycystic ovary syndrome." *Eur* J Endocrinol. Vol. 105, No. 1 (2012 Jan): 166-99.
3. Xie L., et al. "The Effect of Berberine on Reproduction and Metabolism in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Control Trials." *Evid Based Complement Alternat Med.* (2019 Dec 13): 2019-7918631.
4. An Y., et al. "The use of berberine for women with polycystic ovary syndrome undergoing IVF treatment." *Clin Endocrinol (Oxf)*. Vol. 31, No. 3 (2014 Mar): 80-425.
5. Dong H., et al. "The effects of berberine on blood lipids: a systemic review and meta-analysis of randomized controlled trials." *Planta Med*. Vol. 46, No. 6 (2013 Apr): 79-437.
6. Ju J., et al. "Efficacy and safety of berberine for dyslipidaemias: A systematic review and meta-analysis of randomized clinical trials." *Phytomedicine*. Vol. 34 (2018 Nov 15): 50-25.
7. Zamani M., et al. "The effects of berberine supplementation on cardiovascular risk factors in adults: A systematic review and dose-response meta-analysis." *Front Nutr*. (2022 Oct 14): 9-1013055.
8. Zhang L.S., et al. "Efficacy and Safety of Berberine Alone or Combined with Statins for the Treatment of Hyperlipidemia: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials." *Am J Chin Med*. Vol. 767, No. 4 (2019): 47-751.
9. Zhang, Jian, et al. "Preventive Effect of Berberine on Postoperative Atrial Fibrillation." *Circulation: Arrhythmia and Electrophysiology* 15. Vol. 10 (2022): e011160.
10. Zhao J.V., et al. "Effect of Berberine on Cardiovascular Disease Risk Factors: A Mechanistic Randomized Controlled Trial." *Nutrients*. No. 8 (2021 Jul 26): 13-2550.
11. Yin J., et al. "Efficacy of berberine in patients with type 2 diabetes mellitus." *Metabolism*. Vol. 7, No. 5 (2008 May): 57-712.
12. Zhang Y., et al. "Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTE study)." *Nat Commun*. No. 1 (2020 Oct 6): 11-5015.
13. Ming J., et al. "Effectiveness and safety of Bifidobacterium and berberine in human hyperglycemia and their regulatory effect on the gut microbiota: a multi-center, double-blind, randomized, parallel-controlled study." *Genome* Med. No. 1 (2021 Aug 9): 13-125.
14. Zhang H., et al. "Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression." *Metabolism*. Vol. 92, No. 2 (2010 Feb): 59-285.
15. Zhang, Di, et al. "Berberine Containing Quadruple Therapy for Initial Helicobacter Pylori Eradication: An Open-Label Randomized Phase IV Trial." *Medicine*, vol. 96, no. 32, (2017).
16. Tian P., et al. "Leukocytes from diabetic patients kill retinal endothelial cells: effects of berberine." *Mol Vis*. Vol. 105 (2013 Oct 2): 19-2092.
17. Li M., et al. "Improvement of adjunctive berberine treatment on negative symptoms in patients with schizophrenia." *Eur Arch Psychiatry Clin Neurosci*. Vol. 642, No. 4 (2022 Jun): 272-633.