

Berberine ES-5 Duo

Supports a Healthy Glycemic Response*



Clinical Applications

- » Supports a Healthy Glycemic Response to Foods*
- » Helps Support Healthy Blood Glucose Levels*
- » Supports Healthy Insulin Sensitivity*
- » 5× the Bioavailability of Berberine*

*Berberine ES-5 Duo features dihydroberberine (DHB), a highly bioavailable metabolite of berberine with demonstrated benefits for blood glucose metabolism, and InSea2®, a blend of polyphenols derived from sustainably harvested, wildcrafted brown seaweed shown to support a healthy glycemic response to food.**

Discussion

Dihydroberberine (DHB)

Berberine is an alkaloid derived from several botanical species that have been used in Ayurveda and traditional Chinese medicine for various therapeutic applications. Modern clinical use and published in vivo, in vitro, and animal research studies demonstrate that berberine supports healthy blood glucose metabolism and dihydroberberine (DHB), a metabolite of berberine, is a more bioavailable form of berberine with the same beneficial effect.*¹⁻⁶

Berberine absorption across the intestinal epithelia is suggested to be compromised because of its “flat” chemical configuration. It displays poor bioavailability and increased potential for gastrointestinal distress at the oral doses required to improve biomarkers associated with glucose homeostasis. The structure of the DHB derivative of berberine is comparably open, making it more amenable to uptake.³ A study in rodents found that berberine had to be administered at nearly a 5-fold increased dose (560 mg/kg/d) to establish the same effects on glucose metabolism as demonstrated by DHB (100 mg/kg/d), indicating that DHB delivers the beneficial metabolic effects of berberine in a more absorbable form and at a lower dose.*⁵

A small, randomized, double-blind, crossover pilot study (N = 5) investigated the absorption kinetics and compared the dosing of berberine and DHB required to achieve peak plasma berberine concentrations. Subjects completed a 4-dose protocol of placebo, 500 mg of berberine, 200 mg of DHB, or 100 mg of DHB. Participants ingested the first 3 doses with meals, followed by an overnight fast, then dose 4 accompanied by a standardized test meal. Blood samples were collected at regular intervals after ingestion and analyzed for berberine, glucose, and insulin levels. Four doses of 100 mg or 200 mg of DHB produced significantly greater concentrations of plasma berberine across the 2-hour measurement window than a 500-mg dose of berberine or placebo. Results suggest that irrespective of dose, DHB achieves a greater area under the curve (AUC) and peak berberine concentration when compared with oral ingestion of berberine.*⁶

Gut microbiota play a role in reducing berberine to DHB, its intestine-absorbable form. After absorption into intestinal tissues, DHB is

oxidized back to berberine before entering the blood.⁴ Increasing evidence indicates that gut microbiota are crucial mediators regulating berberine’s pharmacokinetic and biological effects. Berberine induces compositional alterations in gut microbiota and regulates gut microbe-dependent metabolites, factors that contribute to its biological effects on lipid and glucose metabolism.*^{7,8}

Although the mechanisms underlying the beneficial effects of berberine for healthy glucose metabolism are not entirely clear, results from animal and in vitro studies suggest that berberine moderates glucose metabolism through a multi-pathway mechanism, including the adenosine monophosphate-activated protein kinase, c-Jun N-terminal kinase, and peroxisome proliferator-activated receptor- α pathways.^{2,9} Berberine is also believed to be involved in the regulation of pancreatic β -cell function, and it has been observed to inhibit the expression of disaccharidases in the duodenum, resulting in less glucose formation from carbohydrate digestion.¹⁰

Clinical trials examining the effects of supplemental berberine in blood glucose management have focused primarily on subjects with diabetes and not the healthy population. However, berberine has also been studied in subjects with the transient condition known as prediabetes. In a randomized trial, subjects (N = 34) with prediabetes were assigned to either a treatment group that received 500 mg of berberine or placebo 3 times daily. Supplementation was found to significantly reduce several markers of glycemic control and insulin resistance, resulting in values below the prediabetic threshold for fasting plasma glucose (FPG) and HbA1c for the 12-week study period.¹¹ In a similar trial, also in subjects with prediabetes (N = 76), participants were assigned 300 mg of berberine 3 times daily or placebo for 12 weeks, with the addition of dietary and exercise interventions. Subjects receiving berberine treatment demonstrated significant decreases in both FPG and HbA1c compared with those who were given the placebo.*¹²

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*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.

The current body of research has helped to establish a clear relationship between berberine and its metabolite DHB. The role of berberine in supporting healthy glucose metabolism, combined with studies showing enhanced bioavailability of DHB compared with berberine, indicates that DHB may be an advantageous supplemental form. However, additional research that directly compares the physiological impact of DHB with berberine is needed to verify the efficacy.*⁴⁻⁶

InSea2®

The branded ingredient InSea2® is a blend of polyphenols derived from the wildcrafted brown seaweeds *Ascophyllum nodosum* and *Fucus vesiculosus* that are sustainably harvested from the North Atlantic Ocean. InSea2 plays a role in inhibiting α -amylase and α -glucosidase, 2 key enzymes involved in the digestion and assimilation of starch and sugar. InSea2 has shown an effect of reducing postprandial blood glucose levels, improving insulin sensitivity, and supporting optimal blood glucose metabolism.*^{13,14}

A randomized, double-blind, placebo-controlled trial in dysglycemic patients (N = 65) evaluated the effect of InSea2 combined with 7.5 mcg of chromium picolinate on glycemic status over a 6-month period. At the end of the study period, 18.2% of patients in the test group returned to normal glycemic status compared with no change in glycemic status in the placebo group. In addition, a significant number of subjects changed categorization from impaired fasting glycemia to impaired glucose tolerance, suggesting improvement in insulin sensitivity and glycemic status in the test group. Overall, subjects in the InSea2 test group had statistically significant improved markers for glycemic health, whereas the placebo subjects—exposed to the same diet and physical activity program—showed a decline in glycemic health markers.¹³ Further study is needed to determine if the beneficial effects are attributable to InSea2 alone or if combining InSea2 with chromium picolinate or other forms of chromium impacts results.*

A randomized, double-blind, placebo-controlled, crossover study in healthy subjects (N = 23) aged 19 to 59 years examined the impact of InSea2 on postprandial plasma glucose and insulin concentrations. Two 250 mg capsules of InSea2 or placebo capsules were consumed 30 minutes before ingesting 50 g of carbohydrate. Plasma glucose and insulin responses were measured over a 3-hour period post-ingestion. InSea2 was associated with a significant reduction in the incremental insulin AUC and an increase in the Cederholm index of insulin sensitivity, suggesting that InSea2 consumption may modulate insulin homeostasis after ingesting a carbohydrate-rich meal.*¹⁴

Berberine ES-5 Duo contains researched doses of dihydroberberine, a berberine metabolite 5× more bioavailable than standard berberine, and InSea2 complemented with chromium nicotinate glycinate. This formulation aims to support a healthy glycemic response to ingested foods and maintain healthy blood glucose metabolism and insulin sensitivity.*

Berberine ES-5 Duo Supplement Facts

Serving Size: 1 Capsule

	Amount Per Serving	%Daily Value
Chromium (as chromium nicotinate glycinate chelate) ^{S1}	7.5 mcg	21%
Brown Seaweed Blend ^{S2}	250 mg	**
Dihydroberberine ^{S3}	100 mg	**

Other Ingredients: Capsule (hypromellose and water), microcrystalline cellulose, ascorbyl palmitate, and silica.

DIRECTIONS: Take 1 capsule twice daily before meals, or use as directed by your healthcare professional.

Consult your healthcare professional before use. Individuals taking medication should discuss potential interactions with their healthcare professional. Do not use if tamper seal is damaged.

STORAGE: Keep closed in a cool, dry place out of reach of children.

FORMULATED TO EXCLUDE: Wheat, gluten, yeast, soy, animal and dairy products, fish, shellfish, peanuts, tree nuts, egg, sesame, ingredients derived from genetically modified organisms (GMOs), artificial colors, and artificial sweeteners.

S1. Albion is a registered trademark of Balchem Corporation or its subsidiaries.

S2. InSea2 is a registered trademark of innoVactiv Inc.

S3. GlucoVantage is a registered trademark of NNB Nutrition.

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