

BERBERINE



A BREAKTHROUGH IN THE MANAGEMENT OF METABOLIC DISEASE AND HUMAN HEALTH

Berberine is a yellow-coloured alkaloid usually found in the roots, rhizomes, stems and bark of various plants such as barberry, tree turmeric, goldenseal and Oregon grape. Its history of use dates as far back as 3000 years in Ayurveda and Traditional Chinese Medicine.

Berberine has fast become one of the most researched phytochemicals and continues gaining popularity, as is evident through the increased research each year and the 7800 published studies as of 2023. Berberine has various benefits including anti-inflammatory, anti-cancer and anti-microbial properties, but the **focus of the research and interest is on its positive effects on diabetes and metabolic syndrome where it has been clinically proven as an effective treatment**, comparable to commonly prescribed pharmaceuticals such as metformin.

Berberine has been generally regarded as safe and well tolerated and is used by clinicians around the world as a direct treatment and adjuvant. The primary interest of this document is metabolic syndrome and diabetes but this is not the only application of berberine.

- + 7800 Published studies and counting
- + Found to be comparable to pharmaceuticals such as metformin
- + The treatment of metabolic dysfunction
- + Type 2 diabetes, elevated cholesterol, hypertension, fat loss and fatty liver
- + Safe and well tolerated with a long history of use

BERBERINE OVERVIEW

Berberine has multiple actions but the primary one believed to have the greatest impact on human health is its ability to activate AMP-activated protein kinase (AMPK).

AMPK is a metabolic sensor and is regarded as a master regulatory switch for the management of cellular energy balance, growth, survival functions and inflammation. When considering the therapeutic potential of berberine, one should consider the effect of AMPK. AMPK regulates an array of biological activities that normalize lipid, glucose, and energy balance.

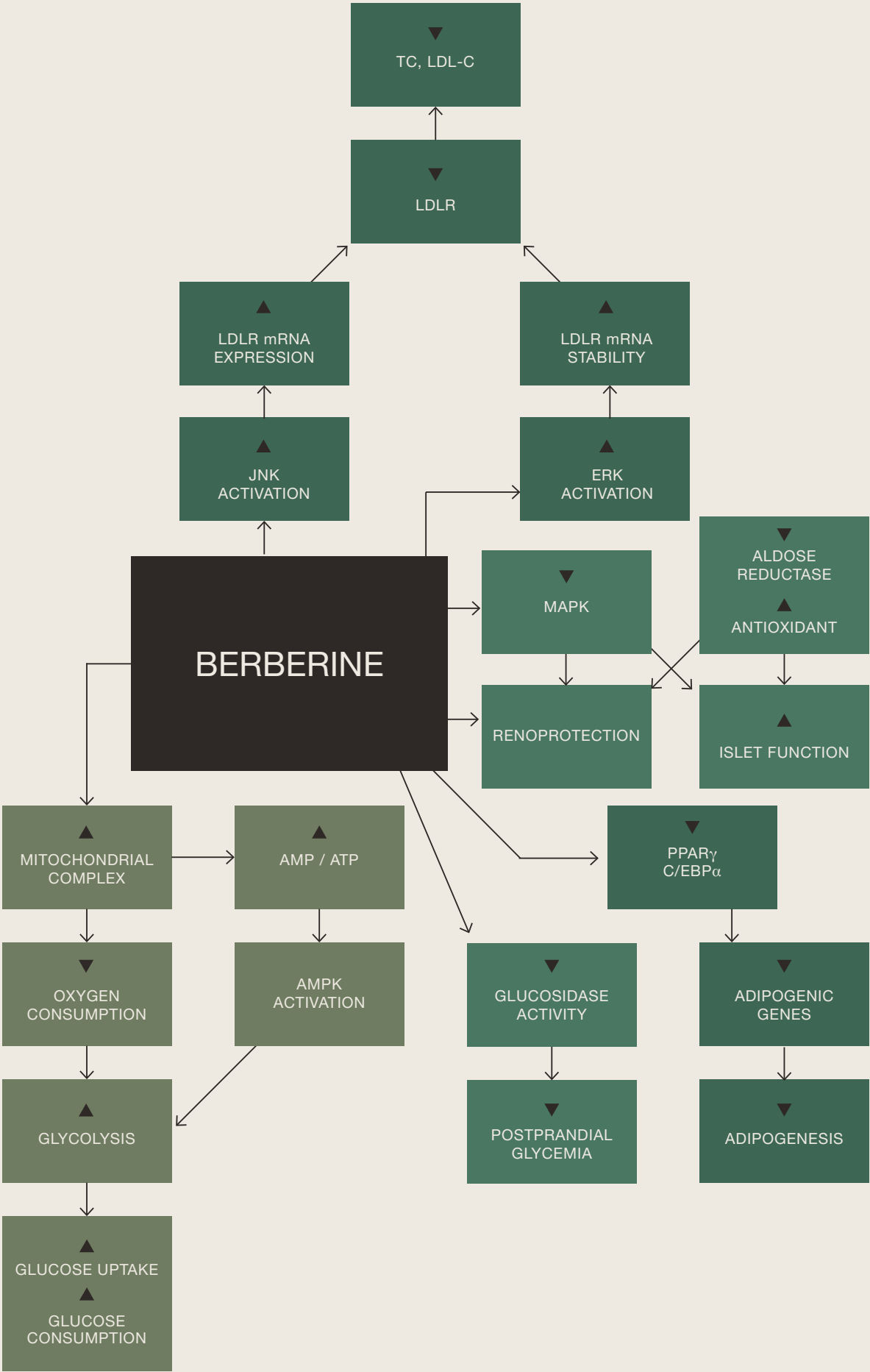
AMPK inhibition is directly linked to metabolic syndrome which is characterized by hyperlipidemia, hyperglycemia, hypertension and excess body fat or waist circumference. It is therefore a key target in the treatment of metabolic syndrome with the activation of AMPK being the principle mechanism of action of the drug metformin. Clinical studies have indicated that berberine and metformin share a similar potency for AMPK activation and are amongst a handful of substances known to have such an effect.

AMPK is activated in the body via leptin and adiponectin – naturally triggered through exercise and dietary energy deficit. It is important to note that excess energy consumption inhibits AMPK, in particular excessive glucose as well as high fat consumption. This is also a key reason why exercise and diet form a part of the effective treatment of metabolic disease.

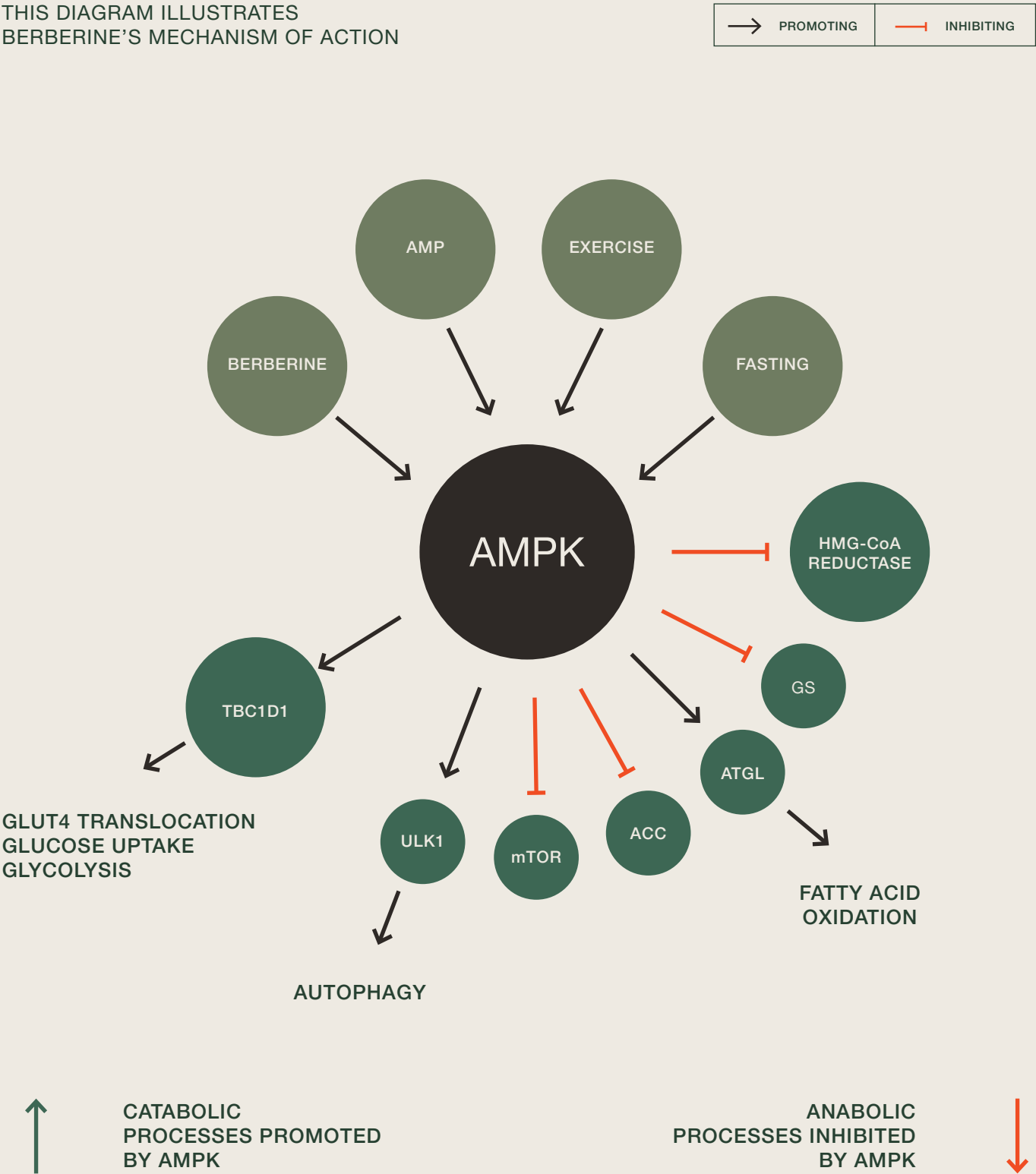
THE GREATEST IMPACT OF BERBERINE
IS ITS ABILITY TO ACTIVATE
AMP-ACTIVATED PROTEIN KINASE



THIS DIAGRAM ILLUSTRATES THE
PATHWAYS THAT BERBERINE ACTS ON



THIS DIAGRAM ILLUSTRATES
BERBERINE'S MECHANISM OF ACTION



Fatty acid oxidation	Fatty acid synthesis
Glucose uptake	Glycogen synthesis
Glycolysis	Gluconeogenesis
Autophagy	Cholestrol synthesis
Mitochondrial biogenesis	

BERBERINE'S MECHANISM OF ACTION

AMPK AND FAT STORAGE

Consumption of excess calories results in increased mTOR activity. This results in unwanted fat storage.¹ mTOR has the opposite effects of AMPK. “Activating AMPK stimulates autophagic breakdown of macromolecular complexes in the cell, thus producing energy and nutrients. In contrast, active mTOR suppresses autophagy to promote cell growth and proliferation”.² Nutrients such as glucose, amino acids, and fatty acids, as well as insulin, growth factors, hormones, and oxygen, all activate mTOR. Consequently, mTOR plays a role in both cellular growth and aging, as well as the regulation of glucose and lipid metabolism. Elevated mTOR levels have been associated with insulin resistance and implicated in type 2 diabetes.³ Elevated mTOR activity leads to the storage of excess calories as adipose tissue. Research indicates that increasing AMPK activity can downregulate excessive mTOR, encouraging cells to store less fat and instead utilize it as an energy source.¹

AMPK AND FAT UTILIZATION

“In response to fasting and exercise, [muscle cells] switch from glucose to fat oxidation for energy, and AMPK is the driving force for that switch”.⁴ Fatty acid oxidation is the metabolic process through which the body converts fats into energy in the form of ATP. AMPK’s ability to enhance fatty acid oxidation is through two distinct mechanisms.¹ First, AMPK regulates Acetyl-CoA carboxylase (ACC) and malonyl-CoA, “alleviating the inhibition on carnitine palmitoyl-transferase which catalyses the entry of fatty acids in mitochondria and constitutes the rate-limiting enzyme of fatty acid oxidation”.⁵ The second explanation is tied to AMPK’s influence on mitochondrial biogenesis. By promoting the generation of more mitochondria, AMPK enhances the capacity for fat oxidation. When this mechanism is coupled with the one mentioned earlier, it has the potential to transform white adipocytes into highly efficient fat-burning entities.

AMPK FOR INSULIN RESISTANCE

AMPK activation increases glucose uptake and lowers fasting plasma glucose levels in type 2 diabetics.⁶ Decreasing levels of AMPK have been linked to insulin resistance. AMPK increases glucose uptake in the muscle through regulation of glucose transporter 4 (GLUT4). When AMPK is activated, GLUT4 translocates to the cellular membrane, creating a doorway for glucose uptake, in muscle cells.¹ AMPK also inhibits the body’s own glucose production (gluconeogenesis).

AMPK INCREASES GLUCOSE UTILIZATION

AMPK promotes glucose utilization by up-regulating glycolysis (glucose breakdown). “AMPK phosphorylates the 6-phosphofructo-2-kinase (PFK 2), a key enzyme of glucose depletion, to activate glycolysis”.⁷

1.

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Burkewitz, K., Zhang, Y., & Mair, W. B. (2014). AMPK at the nexus of energetics and aging. Cell metabolism, 20(1), 10–25. <https://doi.org/10.1016/j.cmet.2014.03.002>

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6.

Steneberg, P., Lindahl, E., Dahl, U., Lidh, E., Straseviciene, J., Backlund, F., Kjellkvist, E., Berggren, E., Lundberg, I., Bergqvist, I., Ericsson, M., Eriksson, B., Linde, K., Westman, J., Edlund, T., & Edlund, H. (2018). PAN-AMPK activator O304 improves glucose homeostasis and microvascular perfusion in mice and type 2 diabetes patients. JCI insight, 3(12), e99114. <https://doi.org/10.1172/jci.insight.99114>

7.

Heidrich, F., Schotola, H., Popov, A. F., Sohns, C., Schuenemann, J., Friedrich, M., Coskun, K. O., von Lewinski, D., Hinz, J., Bauer, M., Mokashi, S. A., Sossalla, S., & Schmitto, J. D. (2010). AMPK - Activated Protein Kinase and its Role in Energy Metabolism of the Heart. Current cardiology reviews, 6(4), 337–342. <https://doi.org/10.2174/157340310793566073>

BERBERINE HYPOGLYCEMIC METABOLIC EFFECT

THE HYPOGLYCEMIC EFFECT OF BERBERINE IS RELATED TO:

+	Regulation of GLUT4
+	Stimulation of glycolysis
+	Inhibition of gluconeogenesis
+	Mitochondrial biogenesis
+	Aldose reductase inhibition

AMPK ACTIVATION POSITIVELY AFFECTS

+	Regulation of mitochondrial function
+	Hyperglycemia
+	Inflammation
+	Hyperlipidemia
+	Hypertension
+	Liver Function
+	Body Fat

CLINICAL EVIDENCE

A meta-analysis from 2015 published in the **Journal of Ethnopharmacology** which included 27 randomized controlled clinical trials involving **2569 patients** concluded that **there was no statistical difference in effect between berberine and oral anti-hyperglycemic drugs**. Berberine was more effective than lifestyle intervention alone or placebo.

For the treatment of hyperlipidemia, berberine with lifestyle intervention was **better than life-style intervention alone**. Berberine with oral lipid lowering drugs was **better than lipid lowering drugs** alone in reducing the level of TC and LDL-C, and raising the level of HDL-C. In a comparative study between berberine and oral lipid lowering drugs, **there was no statistical significance in reducing the level of TC and LDL-C**, but berberine **showed better effect in lowering the level of TG and raising the level of HDL-C**.

NO SERIOUS ADVERSE REACTION WAS REPORTED
IN THE 27 EXPERIMENTS.

Jiarong Lan et al. 2015. Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. *Journal of Ethnopharmacology*, 161: 69-81

STUDY 1

Title:

TREATMENT OF TYPE 2 DIABETES AND DYSLIPIDEMIA WITH THE NATURAL PLANT ALKALOID BERBERINE

Author: Zhang Y et al.
Journal: Metabolic Syndrome and Related Disorders, 2008, 93(7):2559-65
Objective: The objective of the study was to evaluate the efficacy and safety of berberine in the treatment of type 2 diabetic patients with dyslipidemia.
Design: Randomized, placebo-controlled.
Structure: 116 participants with type 2 diabetes and dyslipidemia were split into two groups receiving either 1000 mg of berberine daily or a placebo for 3 months.
Outcome: In the berberine group, fasting and post load plasma glucose decreased from 7.0 +/- 0.8 to 5.6 +/- 0.9 and from 12.0 +/- 2.7 to 8.9 +/- 2.8 mm/liter, HbA1c from 7.5 +/- 1.0% to 6.6 +/- 0.7%, tri glyceride from 2.51 +/- 2.04 to 1.61 +/- 1.10 mm/ liter, total cholesterol from 5.31 +/- 0.98 to 4.35 +/- 0.96 mm/liter, and low-density lipoprotein- cholesterol from 3.23 +/- 0.81 to 2.55 +/- 0.77 mm/liter, with all parameters differing from placebo significantly.

Conclusion:

BERBERINE IS EFFECTIVE AND SAFE IN THE TREATMENT OF TYPE 2 DIABETES AND DYSLIPIDEMIA.

STUDY 2

Title:

THE EFFECT OF BERBERINE SUPPLEMENTATION ON OBESITY PARAMETERS, INFLAMMATION AND LIVER FUNCTION ENZYMES

Author: Asbaghi O et al.
Journal: Clin Nutr ESPEN. 2020 Aug;38:43-49
Objective: To analyse the effects of berberine on anthropometric parameters, C-reactive protein and liver enzymes.
Design: Systematic review
Structure: Databases including EMBASE, Cochrane Library, Google Scholar, MEDLINE, Pubmed and Web of Science were used to search for eligible studies from inception to 30 July 2019. Usable data was extracted and data was pooled by the inverse variance method and expressed as mean difference with 95% Confidence Intervals (95% CI).
Outcome: 12 studies were used in the review. Berberine treatment moderately decreased body weight, body mass index (BMI), waist circumference (WC) and C-reactive protein (CRP) concentrations. However, berberine intake did not affect liver enzymes, including alanine aminotransferase and aspartate aminotransferase (AST).

Conclusion:

THIS META-ANALYSIS FOUND A MODERATE REDUCTION OF BODY WEIGHT, BMI, WC AND CRP LEVELS ASSOCIATED WITH BERBERINE INTAKE WHICH MAY HAVE PLAYED AN INDIRECT ROLE IN IMPROVED CLINICAL SYMPTOMS IN DISEASES WITH METABOLIC DISORDERS. BERBERINE ADMINISTRATION HAD NO SIGNIFICANT EFFECT ON ALT AND AST LEVELS.

STUDY 3

Title:

EFFECTS OF BERBERINE ON LIPID PROFILE IN SUBJECTS WITH LOW CARDIOVASCULAR RISK

Authors: Derosa G et al.
Journal: Expert Opinion on Biological Therapy, 2013, 13(4):475-82
Objective: To evaluate the efficacy as antihypercholesterolemic agent of berberine in patients with low cardiovascular risk.
Design: Double blind, placebo control.
Structure: 144 Subjects, 6 months run in period of diet and physical activity. Participants then received placebo or 500 mg of berberine twice per day for 3 months. Followed by 2 month washout period and then resumed berberine and placebo for a further 3 months.
Outcome: Berberine reduced total cholesterol, triglycerides and LDL cholesterol and increased HDL cholesterol compared with placebo.

Conclusion:

BERBERINE IS EFFECTIVE AND SAFE TO MILDLY IMPROVE LIPID PROFILE IN SUBJECTS WITH LOW RISK FOR CARDIOVASCULAR DISEASE.

STUDY 4

Title:

THE USE OF BERBERINE FOR WOMEN WITH POLYCYSTIC OVARY SYNDROME UNDERGOING IVF TREATMENT

Author: An Y et al.
Journal: Clinical Endocrinology, 2014, 80(3):425-31
Objective: The objective was to evaluate the clinical, metabolic and endocrine effects of berberine vs metformin in PCOS women scheduled for IVF treatment and to explore the potential benefits to the IVF process.
Design: Prospective study. Randomized.
Structure: 150 infertile women with PCOS undergoing IVF treatment. Patients were randomized to receive berberine, metformin or placebo tablets for 3 months before ovarian stimulation.
Outcome: Compared with placebo, greater reductions in total testosterone, free androgen index, fasting glucose, fasting insulin and HOMA-IR, and increases in SHBG, were observed in the berberine and metformin groups. Three months of treatment with berberine or metformin before the IVF cycle increased the pregnancy rate and reduced the incidence of severe ovarian hyperstimulation syndrome. Furthermore, treatment with berberine, in comparison to metformin, was associated with decreases in BMI, lipid parameters and total FSH requirement, and an increase in live birth rate with fewer gastrointestinal adverse events.

Conclusion:

BERBERINE AND METFORMIN TREATMENTS PRIOR TO IVF IMPROVED THE PREGNANCY OUTCOME BY NORMALIZING THE CLINICAL, ENDOCRINE AND METABOLIC PARAMETERS IN PCOS WOMEN. BERBERINE HAS A MARGINALLY HIGHER THERAPEUTIC EFFECT AND ACHIEVED MORE LIVE BIRTHS WITH FEWER SIDE EFFECTS THAN METFORMIN.

STUDY 5

Title:

EFFICACY OF BERBERINE IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Author: Yan HM et al.
Journal: PLoS One. 2015 Aug 7;10(8):e0134172
Objective: A clinical trial was conducted to evaluate the effect of berberine on NAFLD.
Design: A randomized, parallel controlled, open-label clinical trial was conducted in three medical centers.
Structure: 184 eligible patients with NAFLD were enrolled and randomly received (i) lifestyle intervention (LSI), (ii) LSI plus pioglitazone (PGZ) 15 mg qd, and (iii) LSI plus BBR 0.5 g tid, respectively, for 16 weeks.
Outcome: As compared with LSI, BBR treatment plus LSI resulted in a significant reduction of HFC (52.7% vs 36.4%, p = 0.008), paralleled with better improvement in body weight, HOMA-IR, and serum lipid profiles (all p<0.05). BBR was more effective than PGZ 15 mg qd in reducing body weight and improving lipid profile.

Conclusion:

BERBERINE AMELIORATES NAFLD AND RELATED METABOLIC DISORDERS.

STUDY 6

Title:

THE EFFECT OF BERBERINE ON WEIGHT LOSS IN ORDER TO PREVENT OBESITY

Author: Ilyas Z et al.
Journal: Biomed Pharmacother. 2020 Jul;127:110137
Objective: To summarize the previously published clinical studies in vitro, vivo and in humans where the efficacy of berberine has been evaluated in terms of dosage and timing of administration regarding obesity.
Design: Systematic review
Structure: Databases including Pubmed, Scopus and Google Scholar were used to search for eligible studies using specified search terms, within the range of the years 2000 and 2019.
Outcome: 35 studies were included in the review. This review highlighted that berberine effectively prevents the development of obesity through the modulation of gut microbiota, gene regulation, intestinal permeability and Hepatic gluconeogenesis.

Conclusion:

BERBERINE IS NOT ONLY EFFECTIVE FOR OBESITY, BUT ALSO FOR OTHER SYSTEMS AND CONSEQUENCES OF OBESITY SUCH AS DIABETES AND CANCER.

STUDY 7

Title:

EFFECT OF NATURAL PRODUCTS ON COMMERCIAL ORAL ANTIDIABETIC DRUGS IN ENHANCING 2-DEOXYGLUCOSE UPTAKE BY 3T3-L1 ADIPOCYTES

Authors: Prabhakar PK et al.
Journal: Ther Adv Endocrinol Metab. 2011 Jun; 2(3): 103–114
Objective: The management of diabetes with insulin and synthetic oral hypoglycemic drugs (OHDs) can produce serious side effects and in addition fails to prevent diabetes-related complications in many patients. A new diabetes management strategy is needed that is more effective and has fewer side effects.
Method: This paper analyzes the dose- and time-dependent effect of three phytochemicals: berberine, arecoline and vanillic acid, and two antidiabetic drugs: 2,4-thiazolidinedione (TZD) and metformin, on the uptake of 2-deoxyglucose (2DG) by 3T3-L1 adipocytes. The interactions of the phytochemicals with the OHDs were analyzed with isobolograms and the combination index.
Results: TZD and berberine increased 2DG uptake by 3.3-fold (with respect to control) at 15 µM and 25 µM, respectively. The same concentrations of arecoline and vanillic acid increased 2DG uptake by 3.2-and 2.9-fold, respectively, when compared with the basal level. Berberine and arecoline acted synergistically with both the OHDs, whereas vanillic acid had an additive interaction with TZD and an antagonistic interaction with metformin. Arecoline significantly increased the translocation of GLUT4 via the PPAR(y) pathway, whereas berberine and vanillic acid did this via the AMPK-dependent pathway.

Conclusions:

THESE PHYTOCHEMICALS SIGNIFICANTLY REDUCED THE EXPRESSION OF THE ENZYMES INVOLVED IN FATTY ACID AND CHOLESTEROL SYNTHESIS, INDICATING THAT THEY MIGHT HELP PREVENT THE SECONDARY COMPLICATIONS OF DIABETES. THE CURRENT STUDY SUGGESTS THAT BERBERINE AND ARECOLINE COULD ALLOW DOSAGE REDUCTION OF OHDS, WHICH COULD ALSO LEAD TO A REDUCTION IN THE TOXICITY AND SIDE EFFECTS CAUSED BY OHDS.

STUDY 8

Title:

EFFICACY OF BERBERINE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Author: Yin J et al.
Journal: Metabolism Clinical and Experimental, 2008 57(5):712-17. = 2008, 57(5):712-1
Objective: Evaluate the efficacy and safety of berberine as a treatment for type 2 diabetes.
Design: Randomised, two part, comparative human study.
Abstract: In study A, 36 adults with newly diagnosed type 2 diabetes were randomly assigned to treatment with berberine or metformin (0.5 g t.i.d.) in a 3-month trial. The hypoglycemic effect of berberine was similar to that of metformin. Significant decreases in hemoglobin A1c, fasting blood glucose, postprandial blood glucose and plasma triglycerides were observed in the berberine group. In study B, 48 adults with poorly controlled type 2 diabetes were supplemented with berberine in a 3-month trial. Berberine acted by lowering FBG and PBG from decreased. Fasting plasma insulin and HOMA-IR were reduced by 28.1% and 44.7%, respectively. Total cholesterol and low-density lipoprotein cholesterol (LDL-C) were decreased significantly as well. During the trial, 20 (34.5%) patients suffered from transient gastrointestinal adverse effects. Functional liver or kidney damages were not observed for all patients.

Conclusion:

THIS STUDY INDICATES THAT BERBERINE IS A POTENT ORAL HYPOGLYCEMIC AGENT WITH BENEFICIAL EFFECTS ON LIPID METABOLISM.

THERAPEUTIC APPLICATIONS AND POTENTIAL OF BERBERINE

+	Metabolic Syndrome
+	Type 2 Diabetes
+	Dyslipidemia
+	Polycystic Ovarian Syndrome
+	Fatty Liver Disease
+	Diabetic Nephropathy
+	Body Composition & Weight Loss

OPTIMAL THERAPEUTIC DOSING AND SAFETY OF BERBERINE

DOSAGE RECOMMENDATION

Therapeutically, berberine should be taken 2-3 times per day in dosages of 500 mg (+95% berberine alkaloid concentration) at a time. This should be taken before the largest meals of the day and optimally around 30 minutes before eating.

The most popular form of berberine is in the hydrochloride (HCl) form.

Berberine has poor oral bio-availablty with less than 1% reaching plasma. To overcome this, special delivery technologies such as liposomes are used or formulations using the active metabolite - dihydroberberine. Whilst these mechanisms may overcome the issue of absorption into plasma it is understood that berberine has major benefit within the gut via the digestive process itself. This is through positive modulation of the gut microbiome as well as the production of other active metabolites such as columbamine and berberrubine.

Safety: No major side effects have been reported and berberine is well tolerated when using the recommended dosage. Minor gastric upsets were noted in a small percentage of users in the initial stages of safety studies which then passed. Berberine is used by millions of people around the world, both traditionally and now with modern medicine. Whilst berberine has a hypo-glycemic effect, it must be noted that this is only evident in those who have elevated blood glucose levels. The use of berberine should not result in hypoglycemia in those with normal blood glucose levels. In saying this, patients already using pharmaceutical hypoglycemic agents will need to be monitored as berberine may reduce elevated glucose in these patients. The benefit of this is that patients may be able to reduce the amount of medication required or replace it all together.

CAUTION AND CONTRAINDICATIONS

Persons using medications such as anti-hypertensives, anti-hyperglycemics and those with cholesterol lowering effects need to be monitored when using berberine. Berberine will positively affect these conditions and medications may need to be reduced or discontinued.

- **Berberine should not be used concurrently with certain antibiotics (eg. ciclosporin).**
- **Berberine is contraindicated during pregnancy and breastfeeding, especially during the first trimester (first 12 weeks) since it may harm the developing baby.**
- **Safety has not been established in children. Avoid use.**

HOW BEST TO TAKE BERBERINE

1	95% Berberine HCl concentration
2	Liposomal formulation aids absorption and bioavailability
3	Taken 20-30 minutes before largest meals of the day
4	Optimal therapeutic dosing of 500 mg, 2-3 times per day before meals (1000-1500 mg daily)
5	If not managing a chronic condition, cycle berberine: 8 Weeks on, 2-4 weeks off