Clinical Applications of Berberine

In this issue of our newsletter, we provide some updates on the many clinical applications of Berberine, focusing on an article by Jacob Schor, ND, FABNO which appeared in the Journal of Natural Medicine.

Berberine provides significant benefits that we are all aware of for blood sugar management and diabetes (in a similar fashion to Metformin, but with several significant benefits attributable to Berberine that you do not find with Metformin: the key one being cardioprotective benefits).

Int J Clin Exp Med. 2015 Aug 15;8(8):14513-9. eCollection 2015.

Cardioprotective effect of berberine against myocardial ischemia/reperfusion injury via attenuating mitochondrial dysfunction and apoptosis.

Wang Y[1], Liu J[2], Ma A[3], Chen Y[3].

There are however many additional health benefits provided by Berberine which may not be immediately apparent:

Both Berberine and Metformin are also now being identified as potential neuroprotective compounds:

J Mol Neurosci. 2008;34(1):77-87. Epub 2007 Nov 27.

Neuroprotective role of antidiabetic drug metformin against apoptotic cell death in primary cortical neurons.

El-Mir MY[1], Detaille D, R-Villanueva G, Delgado-Esteban M, Guigas B, Attia S, Fontaine E, Almeida A, Leverve X.

ResearchGate:

Neuroprotective effects of berberine on stroke models in vitro and in vivo

Xi-Qiao Zhou, Xiaoning Zeng Nanjing Medical University, Hui Kong, Nanjing Medical University, Xiu-Lan Sun

Here is a list of some additional benefits provided by Berberine:

- AMPK activation
- liver protection (protects against chemotherapy injury)
- anti-inflammatory
- anti-angiogenesis
- anti-depressant
- anti-Alzheimer's disease - Berberine helps prevent oxidation damage to biomolecules in the brain, inhibits enzymes which breakdown important memory molecules, reduces peptides that interfere with proper memory function, and lowers lipids that interfere with cerebral blood flow. Together, these capacities suggest that berberine may act as a promising multipotent agent to combat Alzheimer's Disease
- anti-bacterial
- anti-viral
- anti-parasitic
- antimicrobial action against bacteria, fungi, protozoa, viruses, helminthes, and Chlamydia
- anti-osteoporosis
- anti-rheumatoid arthritis
- anti-diabetic - berberine has many of the same effects as metformin (i.e. AMP kinase activator, increases insulin sensitivity, improves insulin resistance, decreases gluconeogenesis, reduces glucose absorption in the gut, etc.
- the anti-diabetic effects of berberine are the most remarkable: when taken by people with diabetes, berberine appears to be as effective at reducing blood glucose, serum insulin, and HbA1c as the pharmaceutical metformin at the same doses
- anti-cancer (causes cancer cell death, slows cancer growth and increases the effectiveness of radiation therapy and chemotherapy)
- Inhibits the development of cancer from carcinogen exposure
- promotes weight loss
- cholesterol & triglyceride lowering (in one randomized study: lowering triglycerides by 36%, LDL cholesterol by 21%, and total cholesterol by 18%)
- anti-hypertension
- improves post-operative ileus
- protects against radiation-induced gastrointestinal symptoms reduces colitis
- Individuals who consumed berberine in two studies had weight loss of roughly 6-13% over just 3 months
- it also appears to reduce circulating cholesterol levels, which sets it apart from the pharmaceutical drug metformin (which cannot boast the same)
- also, it slows down the release of fatty acids, which cause lipid levels to decrease
- lower lipid levels which helps to prevent harmful fat formation
- strong anti-oxidant properties

- may impact on such auto-immune conditions as rheumatoid arthritis, MS etc. through its action on segmented filamentous bacteria (which have been implicated to potentially initiate changes in the immune system which can lead to an auto-immune response)

Biotics offers two formulations which include Berberine:

Berberine HCl

Bio-HPF Canada

Following is the article by Jacob Schor

Regards,

Rob Lamberton

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"The Best of Science and Nature"

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Potential therapeutic applications in metabolic syndrome, type 2 diabetes, and dyslipidemia

By Jacob Schor, ND, FABNO

About the Author

Jacob Schor ND, FABNO, is a graduate of National College of Naturopathic Medicine, Portland, Oregon, and now practices in Denver, Colorado. He served as president to the Colorado Association of Naturopathic Physicians and is on the board of directors of both the Oncology Association of Naturopathic Physicians and the American Association of Naturopathic Physicians. He is recognized as a fellow by the American Board of Naturopathic Oncology. He serves on the editorial board for the *International Journal of Naturopathic Medicine, Naturopathic Doctor News and Review (NDNR)*, and *Integrative Medicine: A Clinician's Journal*. In 2008, he was awarded the Vis Award by the American Association of Naturopathic Physicians. His writing appears regularly in *NDNR*, the *Townsend Letter*, and *Natural Medicine Journal,* where he is the Abstracts & Commentary editor.

Abstract

New clinical applications for the alkaloid berberine have come to light in recent years. Applications related to adenosine monophosphate-activated protein kinase (AMPK) activation and berberine's possible therapeutic use in metabolic syndrome, type 2 diabetes, and dyslipdemia are reviewed in this article. Potential applications related to cancer are not discussed here but are reserved for a second review.

Introduction

In recent years, the botanical extract berberine has been pushed from relative obscurity to front and center on our supplement shelves due to newly published research. Over a third of the approximately 2,800 studies on berberine listed on PubMed were published in the last 5 years. These studies reveal that berberine may have clinical applications in a range of conditions.

The chemical berberine is found in a handful of plants widely used in botanical medical practice including Goldenseal (*Hydrastis canadensis*), Oregon grape (*Berberis aquifolium*), Barberry (*Berberis vulgaris*), and Chinese Goldthread (*Coptis chinensis*). Two other berberine-containing plants that are familiar to practitioners of Chinese medicine are *Phellodendron chinense* and *Phellodendron amurense*.

Berberine is yellow in color, and plants containing berberine often have been used as a dye, particularly for coloring wool. Chemically, berberine is classified as an isoquinoline alkaloid.

For the past 15 years, our understanding of berberine has been based on an article written by Tim Birdsall and Greg Kelly that was published in *Alternative Medicine Review* in 1997.[1] These sagacious colleagues focused on the relatively short list of actions of berberine that were known at the time:

1. Antimicrobial action against bacteria, fungi, protozoa, viruses, helminthes, and Chlamydia
2. Antagonism against the effects of cholera and E coli heat-stable enterotoxin
3. Inhibition of intestinal ion secretion and of smooth muscle contraction
4. Reduction of inflammation
5. Stimulation of bile secretion and bilirubin discharge

At the time the article was written, berberine was assumed to be useful for the treatment of infectious gastritis, and for many years berberine was placed on the pharmacy shelf where supplements for “GI complaints” were found. These days, berberine may deserve a shelf of its own.

There are 3 general conditions for which we should consider berberine: metabolic syndrome, inflammation, and cancer. This review will cover the first of these 3 conditions, metabolic syndrome.

AMPK Activation

The fundamental mechanism of action underlying berberine’s impact on human health is probably its action on the adenosine monophosphate-activated protein kinase or AMP-activated protein kinase (AMPK). To understand what berberine does, one must first understand AMPK.

This enzyme acts as the central energy regulatory control switch regulating how energy is produced and used in the body. AMPK induces a cascade of events within cells that are all involved in maintaining energy homeostasis. The AMPK system senses and responds to changes in energy metabolism both on the cellular and the whole-body level. It is via AMPK that low energy status switches cellular metabolism from ATP-consuming anabolic pathways to ATP-producing catabolic pathways.

AMPK regulates an array of biological activities that normalize lipid, glucose, and energy imbalances. Metabolic syndrome (MetS) occurs when these AMPK-regulated pathways are turned off, triggering a syndrome that includes hyperglycemia, diabetes, lipid abnormalities, and energy imbalances.[2]

AMPK has been proposed as a target for drug monotherapy treatment of metabolic syndrome. Current MetS treatment typically employs 3 to 5 different medications to manage the different comorbidities such as hyperglycemia, hypertension, hyperlipidemia, and inflammation.3

In theory, a single medication that activates AMPK could replace all of the medications used to treat these various aspects of MetS. Rather than treating symptoms, controlling the AMPK switch may control the entire gamut of metabolic syndrome symptoms.[4]

AMPK helps coordinate the response to these stressors, shifting energy toward cellular repair, maintenance, or a return to homeostasis and improved likelihood of survival. The hormones leptin and adiponectin activate AMPK. In other words, activating AMPK can produce the same benefits as exercise, dieting, and weight loss—the lifestyle modifications considered beneficial for a range of maladies.

While AMPK is activated by energy depletion, it is inhibited by energy excess.

High glucose and glycogen levels inhibit AMPK. This inhibition leads to many of the long-term consequences of diabetes. Exercise and caloric restriction activate AMPK, and this explains their benefit in treating diabetes. High fat intake also inhibits AMPK.

One way to appreciate berberine's potential is to think of it as having the same effect on a patient as increasing exercise while at the same time restricting calorie intake. Think of the effects of AMPK suppression as similar to those of eating a high-calorie diet while leading a very sedentary lifestyle.

Only a few chemicals are known to activate AMPK. Berberine is one of them. Reports that berberine activates AMPK were first published in 2006.[5] Resveratrol, salicylate, and metformin also activate this chemical pathway.[6,7]

AMPK activation was cited early on as an explanation of berberine's ability to improve glucose control in diabetic animals. Berberine increases glucose uptake by muscle fibers independent of insulin levels.[8]

Berberine triggers AMPK activation and increases glycolysis, leading to decreased insulin resistance and decreased oxygen respiration.[9] The same mechanism leads to a reduction in gluconeogenesis in the liver.[10] AMPK activation also explains why berberine has an antiatherosclerotic effect in mice.[11] The same mechanism is reported to underlie berberine's antiobesity effects and favorable influence on weight loss.[12]

Caloric restriction and increased exercise also affect the likelihood of one contracting cancer.[13] Thus it is understandable that berberine-induced AMPK activation is cited for some of its anticancer effects—for example, berberine's ability to inhibit metastasis of melanoma cells.[14] Berberine's ability to blunt and suppress proinflammatory responses is also mediated through AMPK activation.[15] There is such a significant amount of published and ongoing research into berberine's anticancer potential that I have chosen not to cover it in this review but instead to review it specifically at a later time.

One way to understand berberine's action in diabetes is to consider the actions of metformin, a common pharmaceutical drug that is also an AMPK activator.[16] Metformin activates AMPK to a similar degree as berberine, and as a result, they affect metabolism similarly. So it should be no surprise that, like metformin, berberine appears useful for treating type-2 diabetes.

Berberine has been used successfully to treat experimental diabetes in test animals.[17,18] It has also been used to treat type-2 diabetes in human trials.[19–22]

There are 3 general conditions for which we should consider berberine: metabolic syndrome, inflammation, and cancer.

Wang reported in 2009 that berberine (100 mg/kg) restored the vascular endothelial function by increasing nitric oxide levels in rats in which diabetes had been induced by a combination of high-fat diets and treatment with streptozotocin.[23] Wang et al reported similar benefits in a similar rat model in 2011. In this case, the diabetic rats were treated with ascending doses of berberine: 0 (control), 50, 100, and 150 mg/kg/d of berberine for 6 weeks. The hypoglycemic effects of berberine were evidenced in the fasting blood glucose levels and insulin-sensitizing effects.[24]

In 2008, Yin reported the results of 2 human trials in the journal Metabolism on patients newly diagnosed with type-2 diabetes who were randomly treated to take either berberine or metformin (500 mg 3 times a day) in a 3-month trial. The hypoglycemic effect of berberine was similar to that of metformin. In the first study (n=36), the hypoglycemic effect of berberine was similar to metformin with a 2% decrease in A1c (P<0.01) and fasting blood glucose (-8.7 mmo/L, P<.01). In the second study (n=48), patients with poorly controlled type-2 diabetes took berberine for 3 months. Hemoglobin A1c decreased from 8.1% to 7.3% (P<.001).[25]

A recent meta-analysis by Dong et al combined data from 14 randomized trials involving 1,068 participants. Treatment with both berberine and lifestyle modification showed significant hypoglycemic and antidyslipidemic benefits. The effects did not differ from those obtained by the standard hypoglycemic drugs metformin, glipizide, or rosiglitazone.[26]

Berberine has been studied and shown to be effective in treating other conditions that respond to metformin.

In January 2012, the *European Journal of Endocrinology* published results of a clinical trial that found berberine compared favorably with metformin when used to treat women (n=89) with polycystic ovary syndrome (PCOS).[27] A year earlier, an article in Fertility and Sterility reported that berberine reduces insulin resistance in ovarian theca cells and decreased their excessive testosterone production.[28]

Berberine, like metformin, appears to be useful for treating metabolic syndrome. Not only does it reduce insulin resistance but it also normalizes the lipid profiles characteristic of the condition.[29]

Berberine, like metformin, can help reduce the side effect of weight gain triggered by antipsychotic medications.[30, 31]

Researchers have become intrigued by the potential benefit metformin has in treating cancer. It is possible that berberine will have a parallel action.

Berberine increases expression of insulin receptors and so reduces insulin resistance.[32,33] A 2009 study in China suggested that a synergistic action occurs when berberine is combined with metformin or 2,4-thiazolidinedione (THZ) (a peroxisome proliferator-activated receptor [PPAR] activator used to treat diabetes) and might allow a reduction in the amount of these drugs required for treatment and so reduce the risk of toxicity.[34]

If one thinks of AMPK activation as “something that reverses metabolic syndrome,” then several other aspects of metabolic syndrome and potential actions for berberine come to mind. Aside from hyperglycemia, there are 3 other hallmarks of metabolic syndrome: dyslipidemia, fatty liver, and inflammation.

Berberine has a positive impact on all 3.

Lipid Profile

A December 2004 article described berberine as “a novel cholesterol-lowering drug” that worked through a “unique mechanism distinct from statins.” The authors had given berberine to 32 hypercholesterolemic patients for 3 months. The treatment reduced serum cholesterol by 29%, triglycerides by 35%, and LDL-cholesterol by 25%.[35]

A 2009 study reported that in rats, AMPK activation triggered by berberine prevented the development of fatty liver.36 This was followed in 2011 by a randomized controlled trial of 60 humans with fatty liver disease. The tracking of numerous biomarkers showed that 3 months of "berberine can obviously improve the conditions." Liver ultrasounds of the study participants showed a 70% improvement. Total cholesterol and triglycerides also decreased significantly in this trial. These patients took 0.5 g of berberine twice per day.[37]

According to a randomized controlled trial conducted in 2008 with diabetic rats in which dyslipidemia had been induced with a combination of streptozotocin and a high-fat diet, "Berberine reduced diabetic rats' body weight, liver weight and liver to body weight ratio. Berberine restored the increased blood glucose, hemoglobin A1c, total cholesterol, triglyceride, low density lipoprotein-cholesterol, apolipoprotein B and the decreased high density lipoprotein-cholesterol, apolipoprotein AI levels in diabetic rats to near the control ones. Berberine alleviated the pathological progression of liver and reverted the increased hepatic glycogen and triglyceride to near the control levels."[38]

A 2010 human clinical trial analyzed changes in serum metabolites, particularly free fatty acid levels, in 60 patients with type-2 diabetes who had taken berberine. The berberine group had significantly lower levels of free fatty acids, chemicals that are toxic to the pancreas and linked with insulin resistance.[39,40]

Berberine's lipid-lowering mechanism of action is different from that found in the statin drugs.[41] Combining berberine with statin drugs has a synergistic effect and is more effective than using either alone. In 2008, a Chinese researcher reported in the journal Metabolism results of a study that combined berberine with simvastatin. The researchers began by treating hyperlipidemic rats with a combination of both agents together or as monotherapies; the combination of both agents reduced cholesterol by 46% while simvastatin alone reduced cholesterol by 28% and berberine alone by 27%. Combination therapy was then tried on 63 hypercholesterolemic patients. The combined therapy lowered LDL cholesterol 32% more than either monotherapy. Similar benefits were seen with total cholesterol and triglycerides.[42]

Similar synergistic action was seen in an experiment using hyperlipidemic hamsters and treating them with a combination of berberine and plant stanols.[43]

While improving lipids may improve cardiovascular disease (CVD) risk, berberine has other beneficial actions that lower CVD risk. It improves arterial endothelial function and suppresses proinflammatory cytokines, actions that should improve heart health.[44–48]

Adding berberine to cultures of human macrophage–derived foam cells, which had been induced by oxidized LDL, significantly inhibits the effect of oxidized LDL in a dose- and time-dependent manner and inhibits the expression of its lectin-like receptor (LOX-1) actions suggesting that berberine could be useful in treating atherosclerotic diseases.[49]

A July 2003 study published in the American Journal of Cardiology examined the use of berberine in congestive heart failure (CHF). The authors randomly divided 156 patients with CHF into 2 groups. All patients were treated with conventional therapy but 1 group of 79 patients was also given berberine at a dose of 1.2 to 2.0 grams per day. After 8 weeks of berberine treatment, "there was a significantly greater increase in left ventricular ejection fraction, exercise capacity, improvement of the dyspnea-fatigue index, and a decrease of frequency and complexity of VPCs [ventricular premature complexes] compared with the control group. There was a significant decrease in mortality in the berberine-treated patients during long-term follow-up (7 patients receiving treatment died vs 13 on placebo, P<.02)." Proarrhythmia was not observed, and there were no apparent side effects."[50]

Aldose Reductase

A second chemical pathway of interest when considering therapeutic applications of berberine to diabetes is the aldose reductase pathway. Aldose reductase is the rate-limiting enzyme in the polyol pathway. It reduces glucose to sorbitol using NADPH (nicotinamide adenine dinucleotide phosphate) as a cofactor. Sorbitol is then metabolized to fructose by sorbitol dehydrogenase.

In healthy people, only a small amount of glucose (less than 3%) moves through this pathway. However, in the presence of high glucose levels, as much as 30% of total glucose will follow this path. In diabetics, this abnormal flow of glucose down the polyol pathway leads to the accumulation of large amounts of sorbitol, which in turn leads to both osmotic and oxidative stress in the tissues where sorbitol accumulates.[51] Aldose reductase plays a significant role in much of the pathology caused by diabetes, including diabetic neuropathy, retinopathy, and nephropathy.[52]

Lee's 2002 report in the Journal of Agriculture and Food Chemistry revealed that berberine is an aldose reductase inhibitor.53

In 2 separate articles published in 2008, Liu reported that berberine extracts protected or helped repair the kidneys of diabetic mice partly through aldose reductase inhibition.[54,55] Berberine reduced oxidative stress in the kidneys.[56]

Aldose reductase plays a role in diabetic cataract formation, and inhibition helps prevent cataract formation.[57]

Because of these properties, berberine alkaloids "would clearly have beneficial uses in the development of therapeutic and preventive agents for diabetic complications and diabetes mellitus."[58]

A number of other chemical pathways have been delineated that underlie berberine's antidiabetic actions. Berberine inhibits dipeptidyl peptidase-4 (DPP IV) and human protein tyrosine phosphatase 1B (h-PTP 1B).[59] It suppresses production of intestinal disaccharidases, reducing sugar digestion and absorption.[60]

It improves glucose metabolism by inducing glycolysis.[61] It also increases glucose transporter-4 (GLUT-4) and glucagon-like peptide-1 (GLP-1) levels.[62] The peptide GLP-a is more commonly known by the name incretin.[63] Historically, incretin is the first hormone to have been identified. It is secreted by the small intestine after eating and triggers release of insulin. Exenatide (Byetta) and liraglutide (Victoza), both incretin mimetics, have been developed and are now prescribed to treat type-2 diabetes.[64]

Absorption

Berberine was thought to be poorly absorbed across the gut wall. Pharmacokinetic researchers have certainly found low plasma concentrations—levels so low that "the remarkable variety of pharmacological effects exerted by Ber[berine] at blood concentrations below the effective dose required for activity in vitro has been regarded with considerable skepticism."[65]

The pharmacokinetics of berberine are "obscure because plasma concentrations after p.o. administration are too low to detect using general analytic approaches such as HPLC."[66] As a result, it had been assumed that very little if any berberine is absorbed.

It now appears that the situation is more complex; berberine actually appears to be well absorbed. The confusion lies in the fact that it is quickly metabolized. Blood clearance is so fast and biotransformation in the liver so rapid that berberine disappears from the blood faster than it can be measured. Berberine metabolites may be responsible for berberine's biological action.

Most berberine is metabolized in the liver through phase I demethylation and phase II glucuronidation, after which the metabolites are excreted with the bile.

Considerable interest has been directed toward creating nanoparticle delivery systems for berberine, the assumption being that therapeutic effects will increase with increased absorption. These delivery systems fall into 3 general types: solid lipid nanoparticles, nanoemulsions, and liposomes.[67]

Wang et al compared the blood sugar–lowering effect of a nanoemulsion made of phosphatidyl-choline micelles and berberine against intravenously administered and plain oral berberine in diabetic mice. Intravenous injection of a berberine solution lowered blood sugar by 22% while the oral nanoemulsion of berberine lowered blood sugar levels by 57%. The blood glucose–lowering effect of standard oral berberine did not reach statistical significance in this trial.[68]

Results like these are exciting; they suggest the potential for much stronger impact. Enhanced oral delivery systems that could increase the clinical effectiveness of berberine will likely be introduced in the coming years.

What Was Left Out?

This review has by and large ignored several major therapeutic applications for berberine. A second article will review berberine's potential use in treating inflammatory conditions, cancer, depression, and neurodegenerative illnesses.

Conclusion

While the known clinical applications for berberine are diverse and becoming more so over time, there are a few generalizations we might make that will allow us to understand berberine's potential. Berberine activates AMPK in a manner similar to how exercise stimulates increased strength and weight loss. Thus, any condition that would be favorably impacted by a patient losing weight and/or exercising more may be impacted favorably by oral berberine supplementation. It makes sense to consider using berberine in patients with insulin resistance, pre-diabetes, diabetes, metabolic syndrome, hypertension, heart disease, dyslipidemia, cancer, depression, and other neuropsychiatric diseases. We also can look at conditions improved by other AMPK-activating drugs, in particular metformin, to help make educated guesses of other possible applications that may soon be revealed.

Berberine Improves Symptoms of Irritable Bowel Syndrome

The Berberine Story Gets Better and Better

Improves memory, combats antibiotic resistant micro-organisms, reduces smoke-induced lung damage, and fights cancer

Representative Berberine Research

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