**BERBERINE SELECT™ FROM MOSS NUTRITION**

**INTRODUCTION**

One of the most popular supplements in functional medicine and clinical nutrition today is berberine. Why? Probably the main reason is its incredible versatility. It appears to be efficacious for situations ranging from blood sugar/insulin optimization to GI dysbiosis. Interestingly, being so effective for clinical situations that we generally regard as completely unrelated makes berberine somewhat unique in terms of the supplements we tend to employ clinically. How many other supplements can you think of that are effective as both an antimicrobial and an insulin/glucose modulator?

Why is berberine so versatile clinically? As you will see in the following review of the paper “The metabolism of berberine and its contribution to the pharmacological effects” by Wang et al (Wang K et al. Drug Metab Rev, published online ahead of print 2017), the reason has to do with both berberine's somewhat unusual metabolism, compared to many herbs and herbal extracts, and the bioactivity of its metabolites.

The first important point to understand about berberine is that it is not an herb but a bioactive alkaloid that can be found in several herbs:

“Berberine is the principal component for many popular medicinal plants, such as Coptidis chinensis Franch. (family Ranunculaceae), Phellodendron chinense Schneid. (family Rutaceae), and Mahonia bealei (Fort.) Carr. (family Berberidaceae). These traditional medicines were recorded in the Pharmacopoeia of China for their excellent efficacy, including clearing away heat, resolving dampness, purging fire and detoxification.”

Concerning clinical efficacy, the authors provide this overview:

“Berberine, a bioactive alkaloid isolated from several herbal substances, possesses multiple pharmacological effects, including antimicrobial, antidiabetic, anticancer activities.”

However, as was suggested above, this highly versatile efficacy has little to do with the activity of berberine per se. Instead, it appears that berberine's metabolites are responsible for its clinical activity. Wang et al state:

“…berberine undergoes extensive metabolism after oral administration which results in its extremely low plasma exposure. Therefore, it is believed that the metabolites of berberine also contribute a lot to its pharmacological effects.”

How well is berberine absorbed? As you will see in the following quote, quite poorly:

“…berberine has poor absorption in the gut, and most of the oral dose remained inside the gastro-intestinal tract lumen, which was excreted in the feces…”

However, the amount that is absorbed undergoes extensive metabolism and is widely disseminated throughout the body:

“After absorption from the gastrointestinal tract, berberine could be widely distributed in the organs, while its concentration in plasma is low. The part of berberine which was absorbed into the body could be converted into multiple metabolites. In fact, berberine and its metabolites exist simultaneously in vivo.”

**An overview of berberine metabolism**

As an overview, berberine goes through the classic phase I (cytochrome P450) and phase II conjugation metabolism that, as most of you
know, is utilized in the metabolism of many pharmaceuticals and chemical toxins:

“After oral administration, berberine was rapidly metabolized to phase-1 products, which were further conjugated with glucuronic acid or sulfuric acid to form phase-II metabolites rapidly and finally excreted in the urine and bile.”

Of all of the phase-II pathways, it appears that glucuronidation predominant with berberine metabolism:

“In general, berberine phase-1 metabolites are mainly converted into glucuronide conjugates.”

However, the phase-1 metabolites also go through sulfation and methylation:

“Several sulfated metabolites of berberine were found in humans and rats, such as jatorrhizine-3-O-sulfate, demethylberberine-2-O-sulfate and thalifendine-10-0-sulfate.”

Concerning methylation the authors state:

“Usually, berberine could be metabolized to jatorrhizine, which could be subsequently transformed into palmatine through methylation in vivo.”

What organ is primarily responsible for berberine metabolism? As you probably expect, it is the liver:

“…researchers concluded that the liver seemed to be the main metabolic site for berberine.”

What about metabolism in the gut via microflora? Given the low absorption of berberine, it should not surprise you that some of the bioactive metabolites of berberine are formed by gut microflora:

“…the unabsorbed dose will enter the intestinal tract and interact with the gut bacteria. As a result of biotransformation, the structure of berberine was changed and new metabolites were generated, which could exhibit similar pharmacological activities in vivo.”

**Biological activities of berberine metabolites**

As an overview, even though berberine is poorly absorbed, several highly bioactive metabolites will be found in the circulation in significant quantities:

“Even though berberine possesses a really low oral bioavailability, it has exhibited marked biological activities in vivo and the concentrations of its major metabolites such as berberrubine, thalifendine, demethylenberberine and jatorrhizine were at relatively high levels.”

What are the specific clinical effects of berberine and its metabolites? Consider the following:

**Lipids** – “…both berberine and its metabolites have hypolipidemic effects, and columbamine could exhibit marked potential effects on triglyceride-lowering among them.” Similar findings were noted for jatorrhizine. Furthermore:

“…when berberine was given to patients, its metabolites including palmatine, jatorrhizine, columbamine, berberrubine and demethylenberberine might also be active forms together with itself to exert hypolipidemic effects in vivo.”

**Antioxidant activity** – “The OH scavenging activity of berberrubine, a major metabolite of berberine, was investigated using electron spin resonance spectrometry method. At the concentration of 1mM, berberrubine and berberine showed excellent OH scavenging activity with 85% and 23% respectively.”

**Hepatoprotection** – “Demethylenberberine is an essential metabolite of berberine. Recent reports have revealed that demethylenberberine showed hepatoprotective and antifibrotic effects of demethylenberberine in vivo.”

In addition, demethylenberberine has demonstrated hepatoprotective effects in relation to excess ethanol intake. What is the mechanism of this protective effect? Wang et al point out:

“…demethylenberberine could reduce the induction of Cytochrome P450 2E1 (CYP2E1), which has been well documented to be a central pathway that contributes to
ethanol-mediated oxidative stress via reducing the total CYP2E1 protein expression and blocking the distribution of CYP2E1 around the vein. In addition, inducible nitric oxide synthase (iNOS) induced by chronic alcohol consumption in mice which will exacerbate oxidative stress and mitochondrial dysfunction in the liver was also suppressed after demethylenberberine treatment.”

Another berberine metabolite, berberrubine, has also demonstrated hepatoprotective properties by inhibiting lipid peroxidation.

**Hypoglycemic activity** – As many of you know, berberine has excellent, well documented effects on aberrant glycemic metabolism:

“Many publications have shown that berberine exhibited marked antidiabetic effects on both human beings and type-2 diabetic rodent models.”

**Antimicrobial activity** – This is also a fairly well known property of berberine. The authors comment:

“Two of berberine’s metabolites in vivo, palmatine and jatorrhizine (200 and 400 mcg/mL), played antimicrobial roles by inhibition of the growth of bacteria in vitro, such as *Staphlococcus aureus*. Further results also indicated that palmatine and jatorrhizine have shown relatively broad spectrum antimicrobial activities against animal pathogens in vitro, such as *Bacillus cereus*, *Bacillus megaterium*, *Bacillus subtilis*, *Staphlococcus aureus*, *Staphlococcus epidermidis*, *Micrococcus lysodeikticus*, *Proteus vulgaris*, *Salmonella typhi* and *Escherichia coli*…”

In addition:

“…jatorrhizine also exhibited the inhibitory activities against dermatophytes in vitro such as *Trichophyton rubrum* and *Microsporum canis*, indicating jatorrhizine could also be a potential antifungal agent.”

What about candida? I will discuss a study on the impact of berberine on candida shortly.

**Anti-inflammatory properties** – Several berberine metabolites demonstrate anti-inflammatory properties, including jatorrhizine, palmatine, and berberrubine.

**What about toxicity?**

According to Wang et al:

“…it was found that 20.8 berberine/kg of body weight is safe for oral administration in mice, and the safe dose for human would be 2.97 g berberine/kg human body weight because mice have a 7-fold metabolic rate per kg body weight than adult humans.”

Given that the label recommendations for Berberine Select are 1000 mg – 1500 mg (2-3 caps) per day, the chances of ingesting a toxic dose, based on the data above, even if the label dose was doubled, are virtually impossible.

What about adverse effects? The authors state:

“To date, no serious adverse effects have been reported for berberine via oral route in clinic, and it is safe in the majority of human subjects studied in short-term and chronically. However, some transient gastro-intestinal adverse effects have been observed after a high-dose administration of berberine (0.5g, three times a day, in a 3-month trial) for the treatment of type 2 diabetes mellitus patients.”

Therefore, based on the above quote, it should be noted that some selected patients might report some short-term GI distress when ingesting the highest dose recommended on the label of Berberine Select.

**BERBERINE AND CANDIDA**

As we all know, excessive growth of candida in the GI tract is fairly common in our chronically ill patients and can contribute to both GI-related and systemic symptomatology. Therefore, herbs and herbal extracts that have anti-fungal properties such as *Oil of Oregano* (also sold by Moss Nutrition) have long been staples of functional medicine and clinical nutrition practices. As noted by the study “Membrane of Candida albicans as a target of berberine” by Zoric et al (Zoric N et al. *BMC Complementary and Alternative Medicine*, Vol. 17, No. 268, 2017) berberine certainly should be included in this family of substances. The
first quote I would like to feature from this paper highlights the anti-microbial properties of berberine, which includes its impact on candida:

“There is...evidence suggesting that bacteria do not develop resistance to berberine since the minimum inhibitory concentration (MIC) of berberine within the same bacterial cultures (E. coli, S. aureus, Bacillus subtilis, Proteus vulgaris, S. typhimurium and P. aeruginosa) did not increase over 200 generations. Efficacy of berberine against Candida species has encouraged us to investigate further its mechanism of action against C. albicans.”

In this *in vitro* study the following was noted:

“We show that berberine may enter *C. albicans* cell and may act not only from extracellular site but also inside the fungus cell, have significant antifungal activity against *C. albicans* with MIC value of 17.75 µg/mL.”

Zoric et al also noted that berberine can create an apoptotic state in *C. albicans*:

“Data presented indicate that berberine may cause apoptosis in *C. albicans* cells as studies suggest that reactive oxygen species (ROS) accumulation induces and/or regulates the induction of apoptosis in yeasts.”

In the next quote the authors provide more detail on the induction of ROS by berberine inside *C. albicans*:

“Using TBARS assay we showed the accumulation of reactive species including hydroxyperoxides and aldehydes, which are indicators of lipid damage. The significant increase of TBARS in berberine treated cells, and specifically in their membrane preparation, is a sign of an oxidative stress.”

Another way berberine acts on *C. albicans* is by affecting ergosterol synthesis, which is vital for optimal membrane health in candida. Zonic et al point out:

“The effect of berberine on the membrane of *C. albicans* cells was assessed using ergosterol synthesis assay. Berberine modulates ergosterol content significantly (*p* < 0.05) in a concentration dependent manner. At the lowest concentration (1/2 x MIC) berberine caused a 39% reduction in total sterol content, while two other concentrations produced a reduction of 84 and 87%, respectively.”

With the above quotes in mind, it appears that berberine decreases membrane integrity of *C. albicans* in two ways:

- By increasing ROS production which increases lipid peroxidation
- By decreasing ergosterol production

The authors state:

“...berberine may have a dual effect on the lipid peroxidation of the membrane content. Namely, ergosterol is needed not only for maintenance and regulation of the structural and functional integrity of the fungal membrane but also inhibits lipid peroxidation. Thus, since berberine inhibits ergosterol and induces lipid peroxidative stress, it may have an aggregated effect on lipid peroxidation levels in *Candida* cells.”

Finally, the authors discuss other research that demonstrates that berberine can affect mitochondrial activity in one-celled organisms:

“...Dhamgaye and colleagues showed that berberine treatment results in dysfunctional mitochondria, which was evident from its slow growth in non-fermentative carbon source. They also showed poor labeling of treated cells with mitochondrial membrane potential sensitive probe confirming further possible use of berberine as an antifungal drug.”

With the above mind, Zoric et al conclude the following concerning the mechanism of berberine as an anti-candida agent:

“Based on the results presented, we conclude that berberine induces mechanisms involved in its *Candida*-cidal activity probably mainly at the level of the cell membrane. Therefore, it seems that berberine may serve as an alternative for the treatment and/or prevention of candidiasis.”

Now you have a better idea of why Berberine is so useful and why *Berberine Select™ 120 VC* continues to be one of our best selling products.