Recent Clinical Advances with Berberine

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Abstract

Berberine is a constituent in a variety of plants around the world. Berberine-containing plants are used to treat intestinal disorders in many traditions. This use was studied, and, subsequently, isolated berberine was found to be so effective for treating diarrhea that the substance was approved as an over-the-counter diarrheal remedy in China in the 1950s. This article reviews the research on use of berberine for treating congestive heart failure, hyperlipidemia, and type 2 diabetes mellitus. This research suggests that berberine should be more widely used to address these conditions. Berberine is an inexpensive chemical, and virtually every culture has some exposure to berberine-containing plants used in traditional medicine. This wide usage and exposure suggests that berberine is a very safe compound.

Introduction

In this article, we review some interesting research on berberine, an isolated constituent found in various plants around the world. Berberine-containing plants are used to treat intestinal disorders in many traditions. This use was studied, and, subsequently, isolated berberine was found to be so effective for treating diarrhea that this chemical was approved as an over-the-counter diarrheal remedy in China in the 1950s. Today, berberine is widely used to treat diarrhea in China. Research on berberine use for congestive heart failure (CHF), hyperlipidemia, and type 2 diabetes mellitus was largely spurred by clinical observations in China that took place while berberine was used to treat diarrhea. This research is covered in this article.

Isolated Plant Constituents Versus Whole Plants

We are usually proponents of using whole herbs and, as a general rule, avoid using isolated herbal constituents. We value information on the traditional uses of botanicals highly, because long histories of use offer insights accumulated over time on how particular herbs are best used. Traditional use stretching back through time also suggests the safety of those herbs. In addition, isolated antimicrobial constituents have the ability to trigger development of microbial resistance.

A case in point is artemisinin, a constituent in *Artemisia annua* (sweet Annie). Sweet Annie was a traditional remedy for fevers, and, as the plant was studied, scientists, true to the Western paradigm, looked for a "silver bullet." Their research rapidly focused on artemisinin as the plant's active constituent, leading to a fairly widespread use of artemisinin as a malarial treatment. Artemisinin-resistance is now becoming a problem, one that might have been avoided if the constituent had been retained in the whole plant.[1]

To be fair, one should note that artemisinin is often coupled with other antimalarial drugs, but this does not come close to duplicating the complexity of a whole plant that contains artemisinin. For those reasons, we do not recommend widespread use of berberine for treating intestinal infections that may manifest with diarrhea, because microbial resistance is likely to develop over time.

It is already well-established that berberine is a substrate for the multidrug resistance pump, a common molecule expressed by multidrug-resistant microbes.[2] Berberine-containing plants have a long history of use for treating infections, and we see no need to use an isolated constituent in those cases, absent convincing evidence that the traditional whole-plant remedy is less effective.

However, on occasion, research will uncover a new or different use of a plant. *Ginkgo biloba* (ginkgo) is a good example. Researchers uncovered evidence that whole ginkgo leaf enhanced cerebral circulation remarkably. For this research, scientists studied a standardized, concentrated ginkgo leaf extract in which standardization was used to limit the presence of ginkgolic acids in the medicine.[3]

We do not generally embrace standardized herbs except as a manufacturing method of ensuring quality (as opposed to a use intended to ensure activity) because, for the most part, we do not know enough about plant constituents and their syn-

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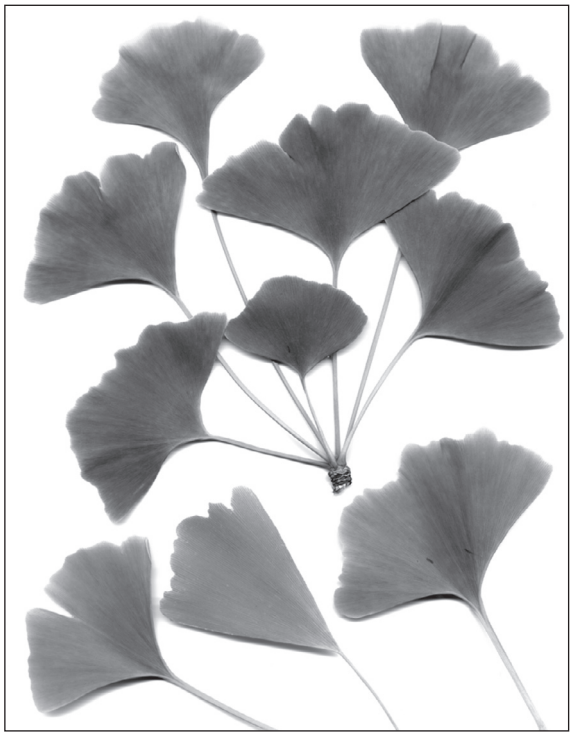


Left: *Ginkgo biloba* (ginkgo); right, *Berberis vulgaris* (barberry).

ergistic interplay to determine that a specific balance of constituents is necessary or appropriate. Nonetheless, we embrace standardized and concentrated ginkgo for that use because a new part of the plant—the leaf—is being used in quite concentrated form in the studies. Without traditional knowledge to guide us, we prefer to follow the research practices that lead us to experiment with a plant's use.

In contrast, German scientists uncovered a new use for an old plant, *Actaea racemosa* (black cohosh). This plant was used traditionally to relieve dull aches and pains. Modern research revealed its potential to help women cope with the menopausal transition.[4] When we use black cohosh, we prefer the nonstandardized whole plant, as we have a wealth of information on using the whole plant and very little (or no) information on why one or another of its constituents should be favored.

Unfortunately, patentable compounds generate greater financial rewards.

In this article, we discuss new or more focused uses for a constituent in fairly well-known plants. We do not examine the use of isolated berberine in a situation in which antimicrobial resistance might arise. Instead, we discuss uses that may have been hinted at in traditional medicine but have been significantly refined by modern research—berberine's applications for treating CHF and hyperlipidemia. Here, we have research on the benefits of the isolated constituent but do not have equivalent information on the use of the whole plant. This has piqued our interest.

Another reason to become familiar with these uses of berberine is that, as berberine is proven safe and effective, research is shifting to the development of synthetic berberine-analogues, usually without any evidence that these new chemicals are superior to berberine itself. Unfortunately, patentable compounds generate greater financial rewards. Berberine is an inexpensive chemical, and virtually every culture has some exposure to berberine-containing plants used in traditional medicine. Given a choice between an effective, naturally occurring, and very safe compound and a new drug developed largely for financial gain, we strongly favor the use of the former.

Berberine in Congestive Heart Failure

Berberine is an example of an alkaloid that is distributed widely in nature and increasingly used in the Orient to treat circulatory and cardiac disorders. While there are hints of traditional use of berberine-containing plants in circulatory disorders, these hints are vague.

The leaf of *Berberis vulgaris* (barberry) was reportedly used in Iran to reduce edema.[5] However, the leaf was not widely used in traditional medicine and contains little berberine. Thus, while the leaf may be effective for addressing edema, it is unlikely that the leaf's benefit results from berberine.

There are also reports that barberry bark, the part used in traditional medicine, has been used as an antihypertensive in France. Finally, berberine-containing plants (most often *Coptis chinensis* [coptis]) were used in Traditional Chinese Medicine

in many formulas that may have been used to treat cardiac disorders. Nonetheless, berberine-containing herbs do seem to have a long-standing use as cardiac treatments, per se. Thus, the research on berberine as a treatment in this area is largely new and interesting.

A most interesting use of berberine is in advanced CHF—a situation in which the heart no longer supplies blood to the body efficiently and available prescription drugs are no longer working satisfactorily. In advanced stages of CHF, any treatment that can increase heart contractility directly and, at the same time, reduce peripheral resistance will be of obvious therapeutic advantage.

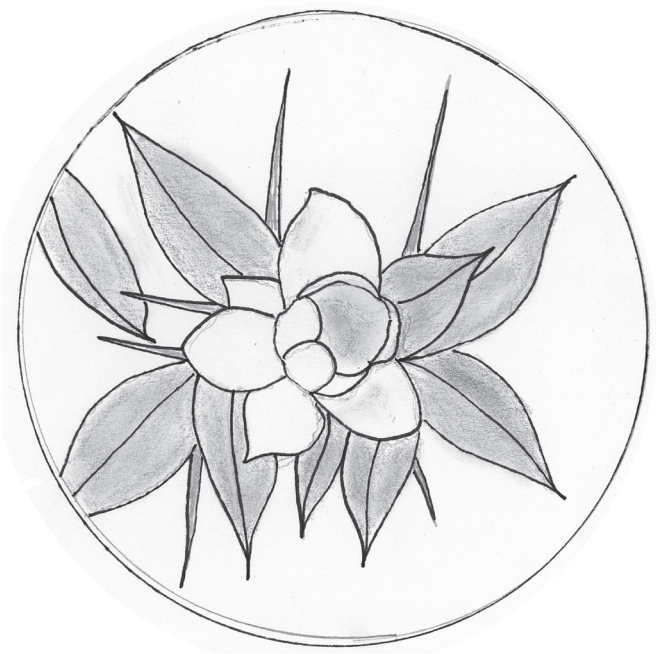
Animal studies have established that berberine lowered peripheral resistance, stimulated cardiac inotropism, and antagonized experimentally induced cardiac dysrhythmias. These results were tested further in a small study of 12 patients with severe CHF that was refractory to conventional medical treatment.[6] Six were class III, six were class IV (according to the New York Heart Association's Classification 1964; Table 1). All were taking digoxin and furosemide, and all had previously unsuccessfully tried vasodilators and angiotensin-converting enzyme (ACE) inhibitors. Two patients were also taking amiodarone and two were taking disopyramide. Berberine was infused intravenously (IV) at a rate of 0.02 mg/kg/minute for 30 minutes, followed by 30 minutes up to 0.2 mg/kg/minute for an additional 30 minutes; the maximum dose delivered was 6.6 mg/kg.

At the outset, all patients had severe left ventricular dysfunction, with low cardiac output, high arteriovenous oxygen difference, and increased vascular resistance. The lower-dose infusion simply decreased heart rate (HR) modestly. In contrast, the higher dose had profound effects: It normalized HR; reduced all cardiovascular pressures; and caused significant increases in cardiac index and significant decreases in systemic and pulmonary vascular resistance. Left ventricular ejection fraction rose and oxygen transport was augmented.

This hemodynamic improvement in these patients was attributed to the result of an effective unloading of both ventricles, combined with stimulation of the inotropic state of the myocardium. Arteriolar vasodilation was deemed responsible for the drop in systemic pressure and resistance. Side-effects were minor, including facial flushing in 2 cases and transient nausea in 2 others. Treatable ventricular tachycardia occurred in 4 patients. No herb–drug interactions were noted in this trial.

Many patients with CHF have cardiac arrhythmias that can be life-threatening. Antiarrhythmic drugs can be dangerous in these patients, probably because the drugs have a negative inotropic effect that can induce coronary artery spasms. Berberine reportedly acts as an antiarrhythmic agent with a positive inotropic effect, while also acting to dilate coronary arteries and inhibit α-adrenergic receptors.

Based on these potential effects, a study of 56 patients was conducted in a hospital setting. The patients had CHF (38 class III and 18 class IV; see Table 1 for classifications), with frequent premature ventricular beats and/or ventricular tachycardia.[7] The patients were initially hospitalized for this study, because the pharmacokinetic properties of orally administered berberine in guinea pigs suggested that plasma levels of berberine might possibly rise to a level high enough to inhibit potassium transport and cause significant adverse effects.



Berberis vulgaris (barberry) Drawing © 2010 by Kathy Abascal, BS, JD, RH (AHG).

The patients continued taking their prescription heart medications; all were taking loop diuretics and angiotensin-converting enzyme (ACE) inhibitors. Fifty-one took digoxin and 46 took nitrates. Patients were given 1.2 g of berberine daily for 2 weeks. All patients had improved left ventricular ejection fraction, with decreased frequency and complexity of ventricular premature beats. The improvement was most significant in patients with a higher plasma berberine concentration.

The researchers did not find excess levels of plasma berberine to be an issue. Instead, they concluded that, because little of the administered berberine ended up in the blood, and, because clinical improvements correlated with adequate plasma levels of berberine, attaining adequate levels made the initial monitoring of berberine levels advisable. No negative drug interactions were noted.

In another study of 156 patients with CHF (47 class II, 78 class III, and 31 class IV) and frequent ventricular precontractions and/or ventricular tachycardia, one group was given 300 mg of berberine 4 times per day, and the other group was given placebo.[8] The individual dose was adjusted weekly to ensure that the active group retained berberine blood levels > 0.1 mg/L with a maximum adjusted dose of 500 mg, 4 times per day. At 8 weeks, cardiac function improved more in the active group.

The active group also had improved 6-minute walking distance and left ventricular ejection fraction, along with a decrease in ventricular premature contractions, ventricular tachycardia, systolic blood pressure (SBP), and diastolic blood pres-

sure (DBP). At 24 months, the active group had fewer hospital admissions and lower total mortality, with a trend toward a lower incidence of sudden cardiac distress. These positive results were not associated with any increase in adverse effects. A previous study by the same group of researchers reportedly found that berberine improved cardiac systolic function and increased cardiac output to a greater extent than digoxin did.[9]

Advanced CHF is a difficult disease to treat. The potential of a safe, inexpensive compound to ameliorate most aspects of this disease is remarkable, and should be embraced although the studies to date are small. This is particularly true, because, apparently, berberine is widely used for treating CHF in China, and more clinical data may exist that are not readily available to us.

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It is of particular interest that no adverse effects were noted in patients taking medications commonly prescribed for CHF. The study researchers recommend that dosing be monitored to ensure that adequate blood levels of berberine are achieved because it is poorly absorbed. Outside of the research setting, this may not be possible, and an initial dose of 500 mg 2 times a day appears to be appropriate based on study results.

In CHF, this dose apparently can be increased to 500 mg 4 times per day, if needed. Ideally, future pharmacokinetic studies would investigate whether adding either whole berberine-containing plants, or other plants traditionally used in combination with them, might improve bioavailability. There is evidence from rodent studies that *Cinnamomum cassia* (cassia) bark increases absorption of berberine from coptis rhizome.[10] This would be similar to a study showing that the saikosaponins in *Bupleurum chinensis* (Chinese thorowax) are made more bioavailable by compounds found in *Panax ginseng* (Asian ginseng), perhaps explaining why these two herbs often are combined in traditional formulas.[11]

Berberine and Hyperlipidemia

The ability of cholesterol-lowering drugs to reduce the morbidity and mortality of CHD remains in question. Nonetheless, the mainstream view is that lower low-density lipoprotein cholesterol (LDL-C) levels slow the progression of atherosclerosis and reduce cardiovascular events in CHD. As a result, cholesterol-lowering drugs are prescribed widely to lower LDL-C levels in patients with the hope of achieving this potential long-term benefit.*

Cinnamomum cassia (cinnamon).

Regardless of the wisdom of this clinical approach, more than half of patients with hypercholesterolemia do not reach their LDL-C goals, even when using statin drugs as first-line therapy.[12] In cases in which statins fail to reduce LDL-C levels adequately, these drugs are often combined with other types of lipid-altering agents, including bile-acid sequestrants, niacin, and ezetimibe. Animal studies show that berberine lowers cholesterol, has a good safety profile, and acts through a mechanism distinct from statins.

In one clinical trial, 63 patients were divided into three groups.[13] For 2 months, patients received 500 mg berberine of 2 times/day, 20 mg per day of simvastatin, or the two agents combined. All groups experienced a significant reduction in LDL-C levels by day 10, with the combination-therapy producing statistically superior results. Berberine alone reduced levels by 23.8%, simvastatin by 14.3%, and the combination by 31.8%. Total cholesterol levels declined in a similar pattern. In addition, berberine alone reduced triglyceride levels by 22.1%, simvastatin by 11.4%, and the combination by 38.9%. No adverse effects were noted.

These data suggest that berberine may be used as a dose-sparing agent for patients experiencing adverse reactions to simvastatin. Berberine also appeared to be potentially superior to Vytorin, as drugs such as ezetimibe often compromise the ability of statin drugs to lower triglycerides.[13] The results also suggest, given that berberine alone was more effective than simvastatin alone, that it might be appropriate to begin treatment with berberine, adding simvastatin if needed. Certainly, at least some patients could completely replace simvastatin with berberine.

*In 2005, 29.7 million people were prescribed statin drugs (see www.statinanswers.com/economics.htm Accessed July 20, 2010).

A recent review analyzed the cardiovascular effects of berberine.[14] In one of the reviewed studies, 32 patients with hyperlipidemia were given 500 mg of berberine 2 times per day for 3 months and were compared with 11 patients who were given placebo.[15] Berberine lowered total cholesterol by 29%, triglycerides by 35%, and LDL-C by 25%. Similar results were obtained in a larger trial of 116 patients, who had both hyperlipidemia and diabetes. The patients were given either 500 mg of berberine 3 times per day or placebo. The patients' serum lipids decreased in a similar pattern to the other study, along with a significant decrease in glycohemoglobin as well as fasting and 2-hour postprandial glucose levels.[16]

Finally, in a study of 40 patients with hyperlipidemia, participants either took berberine alone or in combination with other natural compounds (policosanol and red yeast rice extract) often used to reduce cholesterol levels.[17] Patients either took 500 mg per day of berberine or that dose of berberine along with policosanol (10 mg/day) and red yeast rice extract (3 mg per day) for 4 weeks. The patients' triglycerides dropped by 26% in the combination group versus 22% in the single therapy group. LDL-C was reduced by 25% in the combination group and 20% in the berberine only group, hinting that berberine has a synergistic effect with compounds that inhibit cholesterol synthesis.

Berberine in Hyperlipidemic Patients with Liver Ailments

Statins are not recommended in patients with liver diseases, because statins may affect the function of hepatocytes adversely. Another reason for not recommending statins in these patients is that the liver P450 system is the major route for statin metabolism, raising the risk of elevated blood levels of the drug, in turn, increasing the risk of statin-related adverse effects.

As pharmacologic studies indicated that berberine would be able to reduce cholesterol levels without compromising the liver, a study of patients with hyperlipidemia who also had liver ailments was conducted.[18] Eighty-six patients—51 with hepatitis B (HBV), 18 with hepatitis C (HCV), and 17 with alcoholic cirrhosis—were randomly divided into groups who were treated with berberine (500 mg 2 times per day) or with silymarin (70 mg 3 times per day) for 3 months.

In the patients with HBV, berberine lowered cholesterol by 15.1%, LDL-C by 20.8%, and triglycerides by 20.7%. Silymarin reduced liver enzymes and triglycerides but did not lower total cholesterol or LDL. In patients with HCV berberine lowered cholesterol by 18.6%, LDL by 19.4%, and triglycerides by 20.4%. In patients with cirrhosis, berberine lowered cholesterol by 16.3%, LDL by 22%, and triglycerides by 17.1%. Effects of silymarin on patients with HCV or alcoholic cirrhosis were not reported.

Berberine also reduced levels of alanine aminotranferease (ALT) and aspartate aminotransferase (AST) in patients with either HBV or liver cirrhosis. Based on these results, the researchers stated: "Berberine could be an ideal drug to control lipid metabolism alone or in combination for hyperlipidemic hepatitis or liver cirrhosis patients."[18]

The clinical trials are small. However, the potential benefit of using berberine as a first-line treatment for hyperlipidemia, sparing patients the cost and risks of prescription drugs, is exciting.

Table 1. New York Heart Association Classification Stages of Heart Failure

Class	Patient symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitaion, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitaion, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Table 2. Comparison of Berberine with Conventional Agents[22]

Test value	Berberine	Metformin	Rosglitazone
Fasting blood glucose (FBG)	25.9% reduction	30.3% reduction	17.6% reduction
Glycated hemoglobin (HbA1c)	18.1% reduction	23.4% reduction	18.1% reduction
Triglycerides	17.6% reduction	"Less effect"	"Less effect"
Blood insulin level	28.2% reduction	Not reported	Not reported
Alanine aminotransferase (ALT)	Reduced	Not reported	Not reported
Aspartate aminotransferase (AST)	Reduced	Not reported	Not reported

Berberine and Diabetes

Berberine is also drawing attention for its potential positive effects on patients with diabetes. Using isolated berberine to treat diabetes is interesting, but, in our opinion, less so than using this chemical to treat cardiac disorders. There are many plants with a long tradition of use for treating diabetes that deserve more priority in terms of research, including the berberine-containing plant coptis frequently used in traditional Chinese formulas for addressing diabetes. In fact, a recent reviewer noted that there are ~ 410 experimentally proven medicinal plants with antidiabetic properties, 109 of which the mode of action is known.[19]

Nonetheless, the data on berberine and diabetes are interesting, because berberine may be a very safe treatment option for an increasingly common disorder. There are indications that berberine may prove to be superior to currently used drugs, both in terms of efficacy and safety, and may be a better alternative for people not inclined to prescribe (or use) botanicals.

In China, in the 1980s, berberine's hypoglycemic effect was accidentally discovered when the compound was administered to patients with diabetes who had diarrhea.[5] Subsequent in vitro studies showed that berberine increased insulin sensitivity in human liver cells. In rats, berberine lowered fasting blood glucose levels and fasting blood insulin levels, and increased insulin sensitivity in the liver. These results indicated that berberine had a real potential for treating type 2 diabetes mellitus and metabolic syndrome.[20]

Early clinical studies of berberine were published in Chinese and English but translations could not be obtained for the Chinese studies.[21] However, subsequent studies have been published in English. One investigated 2 groups of individuals with type 2 diabetes[22]: The first group consisted of 97 patients who discontinued all previous therapies 2 weeks before the study started, and then were divided into 3 treatment subgroups. For 2 months, the first subgroup (50) took berberine (1 g per day), the second subgroup (26) took metformin (1.5 g per day), and the third subgroup (21) rosglitazone (4 mg per day; GlaxoSmithKline, Brentford, Middlesex, United Kingdom).† All patients improved. See Table 2 for the results of this part of the study.

The second part of the study tested 35 patients with chronic hepatitis (18 with HCV and 17 with HVB) and type 2 diabetes.[22] This investigation was undertaken because the first-line treatment for diabetes is metformin or rosglitazone, and both of these drugs have potential adverse effects on the liver. A previous study had shown that berberine was both safe and effective in hyperlipidemic patients with chronic viral hepatitis or liver cirrhosis.[23] In the second part of the newer study, patients were treated with 1 g/day of berberine for 2 months. Berberine reduced fasting blood glucose, triglyceride, and ALT, and AST levels in these patients. Based on these results, the researchers concluded that berberine is "an ideal medicine" for patients with type 2 diabetes.[22]

†There was no placebo group because of concern that the patients' conditions might worsen if no treatment was provided.

Another study compared the effectiveness of berberine and metformin, stating that there is a constant need to develop new treatments for type 2 diabetes because all the existing oral hypoglycemic agents fail when administered long term.[24] This study was also divided into two parts. In study A, 36 patients were first treated with diet alone, and then were randomly assigned to receive berberine or metformin. In study B, 48 subjects inadequately treated with diet plus sulfonylureas, metformin, acarbose, or insulin therapy (alone or in combination) participated. Subjects either took 500 mg of berberine 3 times per day at the beginning of each major meal or 500 mg of metformin 3 times per day after major meals. Patients in study B also continued taking their usual medications.

If intolerable gastrointestinal (GI) side-effects occurred, the berberine dose was reduced to 300 mg 3 times per day. The primary endpoint was HbA1c. Secondary measurements included fasting blood glucose (FBG), postprandial blood glucose (PBG), triglycerides, total cholesterol, high-density lipoprotein (HDL), and LDL.

In study A, berberine reduced blood glucose and lipids. Compared with metformin, berberine had an identical effect on regulation of glucose metabolism. Berberine was superior to metformin in terms of its effect on lipid metabolism, with triglycerides and total cholesterol significantly lower than in the metformin group. In study B, berberine reduced FBG and PBG. In the combination therapy for 5 weeks, berberine reduced HbA1c, FBG, and PBG remarkably. Blood lipids were reduced, and waist and waist–hip measurements declined significantly without weight loss.

The studies on berberine in diabetes indicate that berberine would be advantageous as a first-line treatment for type 2 diabetes.

GI issues were fairly common: 21% of patients required a reduction in dose because of adverse GI effects (diarrhea, constipation, flatulence, and abdominal pain). Of these 14, 10 were taking metformin or acarbose with berberine; the rest were also using insulin. There were no severe GI events in patients who were treated with berberine alone. Symptoms disappeared when the dose was limited to 300 mg of berberine 3 times per day. The researchers concluded that berberine was advantageous because of its broad effects, low cost, and overall safety.

The studies on berberine in diabetes do indicate that berberine would be advantageous as a first-line treatment for type 2 diabetes instead of currently used drugs that are more expensive and pose a greater risk of side-effects. We, as mentioned, also think that berberine-containing whole-plant formulas need to be included in these studies. Just as hypoglycemic drugs lose their effectiveness with long-term administration,

berberine may do so as well. It simply appears that cells—human, cancerous, or microbial—develop tolerance more easily to single compounds than to a full arsenal of compounds contained in a whole-plant preparation.

Safety of Berberine

Berberine is not considered toxic at the doses used in clinical situations. It should be avoided in pregnancy because the chemical may stimulate uterine contractions.[5] In vitro, berberine displaces bilirubin from albumin, about ten times more than phenylbutazone, a known potent displacer of bilirubin.[25] Thus, berberine should not be used in jaundiced neonates. It also displaces warfarin, thiopental, and tolbutamide from their binding sites in vitro, increasing blood levels of the free drugs, and potentially enhancing their actions or toxicity. Berberine also appears to elevate blood concentration of cyclosporin A in both healthy patients as well as those who have received renal transplants.[5] However, berberine has been safely co-administered with many different drugs in the studies discussed in this article (e.g., digoxin, furosemide, amiodarone, disopyramide. metformin, rosglitazone, acarbose, and insulin.)

Conclusion

The research on berberine for treating CHF, hyperlipidemia, and type 2 diabetes mellitus is encouraging. This research suggests that berberine should be more widely used to address these conditions. This chemical is inexpensive, compared with conventional agents, and virtually every culture has some exposure to berberine-containing plants used in traditional medicine. This wide usage and exposure suggest that berberine is a very safe compound. ■

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