Berberine: Biochemical Analysis and Cardiovascular Benefits

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ABSTRACT

Berberine is an alkaloid found in plants such as goldenseal (Hydrastis Canadensis L.), European barberry or jaundice berry (Berberis vulgaris L.), and Chinese goldthread or Huanglian (Coptis chinensis Franch.). Goldenseal can be grown in Canada and natural health products derived from this plant have been found on consumer shelves. In this review, a UPLC-based analysis of berberine in a goldenseal product is presented. The linear range for berberine is from 10 to 500 \(\mu\)g/mL with a coefficient of determination \((R^2)\) of 0.9996. Two major cardiovascular benefits of berberine are discussed: lipid lowering and antioxidant effects. Berberine has been shown to lower blood cholesterol through the stabilization of LDL receptor mRNA and to lower triglycerides through activation of AMPK, which in turn, targets two other enzymes involved in lipid biosynthesis, ACC and HMG-CoA reductase. For its antioxidant effects, berberine has been shown to directly scavenge ROS/RNS species, to upregulate endogenous antioxidant defense mechanisms and to inhibit endogenous ROS/RNS-generating oxidases such as NADPH oxidase. Berberine has potential to be used as a complementary therapy for hyperlipidemia and for prevention and management of cardiovascular disease.

Keywords: AMPK, anti-oxidant, lipid-lowering, NADPH oxidase, UPLC analysis

Abbreviations: ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low density lipoproteins; LDLR, LDL receptor; LP, lipopolysaccharide; MAPK/ERK, mitogen-activated protein kinase/extracellular-signal regulated kinase; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; O2•−; superoxide anion; OONO•, peroxynitrite; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; SREBP, sterol regulatory element binding proteins; UPLC, ultra performance liquid chromatography

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INTRODUCTION

Berberine is an isoquinolone alkaloid (Fig. 1) which is found in the fruit, root, rhizomes, stems and bark of plants such as goldenseal (Hydrastis Canadensis L.) (USDA ARS), European barberry or jaundice berry (Berberis vulgaris L.) (USDA ARS), and Chinese goldthread or Huanglian (Coptis chinensis Franch.) (USDA ARS). Previously in Canada, the native goldenseal was a common species found in the deciduous forest of southern and southwestern Ontario (Royal Ontario Museum) but it is now a threatened plant species (Ontario Gov 2009). Currently, goldenseal is listed under the Endangered Species Act of Ontario and there are restrictions in the production of this plant (Filotas et al. 2009). For a more detailed discussion on the cultivation of goldenseal, please refer to the reviews by Sinclair and Catling (Sinclair and Catling 2001; Sinclair et al. 2005).

Extracts and decoctions from the above plants have been used in Chinese and Ayurvedic medicine for many years as treatment for gastrointestinal disorders, liver dysfunction, gallbladder disease and urinary tract infections (Gruenwald 1998; Jellin et al. 2000). Recently, products...
based on goldenseal have appeared in the natural health products or supplements section of many retailers and grocers. As the list of potential therapeutic benefits of berberine grows, there is an increased need to provide valid science-based information to consumers so they are able to make informed choices in their personal healthcare regimen. In this review, the analysis of berberine using a more recent technology in chromatography is discussed. It will also review the lipid-lowering and antioxidant effects of berberine.

ULTRA-PERFORMANCE LIQUID CHROMATOGRAPHY (UPLC) ANALYSIS

There are many reports on the chemical analysis of berberine, with most of them utilizing liquid chromatography combined with mass spectrometry (Weber et al. 2003). Brown and colleagues have just described a validation study of a rapid extraction and the quantitative determination of hydrastine and berberine using high pressure liquid chromatographic techniques in a variety of goldenseal products (Brown and Roman 2008; Brown et al. 2008). Recently, a new liquid chromatography technology – ultra-performance liquid chromatography (UPLC) has been introduced to the analytical and separation science community and it provides improved resolution, speed and sensitivity (Swartz 2005) when compared to traditional high performance liquid chromatography. This chromatography technique is used here to analyze an extract prepared from goldenseal.

Sample extraction

Extraction was performed on goldenseal capsules purchased at a local grocery store and the procedure was similar to that described previously (Brown et al. 2008) with some modifications. Briefly, for 100 mg of sample, 8 mL of extraction solvent was used. The solvent was comprised of 30% acetonitrile, 1% acetic acid, and 69% water. The sample was quickly mixed by vortex prior to sonication for 15 min then centrifuged for 10 min at 2500 × g. The supernatant was filtered with a Pall Acrodisc 0.8/0.2 μm syringe filter and stored at 4°C until analyzed by UPLC.

UPLC chromatography conditions

Samples and standards were analyzed using a Waters Acquity® UPLC system consisting of the photo-diode array detector, binary solvent manager, sample organizer and Empower2 software. Detection was at 280 nm after separation on a Waters UPLC BEH C18 1.7 μm 2.1 × 100 mm column set at 28°C. Samples were diluted in extraction solvent 1:1 and filtered using a Whatman Mini-UniPrep syringeless filter prior to 1 μL injection. The gradient started at 90% mobile phase A (25 mM ammonium formate in water with 0.1% formic acid) and 10% B (acetonitrile) and increased to 50% mobile phase B in 4 min. The gradient was run at 0.4 mL/min and the total gradient run time was 7 min. Fig. 2 shows a typical UPLC chromatographic profile generated from an analysis of the goldenseal sample in comparison to standard compounds obtained from Sigma-Aldrich.

![Fig. 1 Chemical structure of berberine.](image1)

![Fig. 2 UPLC Separation Profile of Goldenseal Extract on an UPLC BEH C18 column at 280 nm. Identification of marker compounds, berberine (red line) and hydrastine (blue line) was based on profile of injected standards. Inset shows spectrum of berberine standard using Waters Acquity PDA Detector (220-500 nm).](image2)
Berberine determination

Standard solution was prepared as described previously (Brown et al. 2008). To calculate berberine content in the samples, an eight-point standard curve ranging from 10 to 500 μg/mL was generated. Over this range, quantitation of berberine was linear (correlation coefficient, R² = 0.9996). The amount of berberine in the sample was determined to be an average of 3.68 (%w/w) with a standard deviation of ±0.01%.

LIPID-LOWERING EFFECTS

Berberine has recently begun to gain attention for its lipid-lowering properties, particularly in regards to its effect on cholesterol and triglycerides metabolism. Its potential as a new therapy for hyperlipidemia is under investigation. The current most commonly prescribed and highly effective lipid-lowering drugs are the statins, which act by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. The primary goal of statins is to lower plasma cholesterol, which is mainly carried by low-density lipoproteins (LDL) in the circulation. Cholesterol metabolism genes are under the control of a family of transcription factors, the sterol regulatory element binding proteins (SREBP), which are anchored in the endoplasmic reticulum in their inactive form. Under conditions of low intracellular cholesterol, SREBP are cleaved and the cytosolic N-termini enter the nucleus, where they bind target gene promoters and stimulate gene expression. HMG-CoA reductase and LDL receptor (LDLR) are among the genes up-regulated by SREBP (Horton et al. 2002). The inhibition of HMG-CoA reductase by statins and the subsequent decline in intracellular cholesterol results in an increase in LDLR expression via SREBP activation, which brings about improved clearance of plasma LDL-cholesterol through LDLR-mediated endocytosis (Goldstein and Brown 2009). Hypercholesterolemia is recognized as a major risk factor for atherosclerosis (Canto and Iskandrian 2003; Nabel 2003). Lowering plasma LDL-cholesterol has been strongly associated with a decreased risk of developing cardiovascular disease in humans (Grundy 1998; Ansell et al. 1999). Berberine has been shown to regulate lipid metabolism by two mechanisms different from the manner in which statins act.

Effects on cholesterol

Berberine’s ability to lower cholesterol is believed to occur through the stabilization of LDLR mRNA, leading to an increase of LDLR on the hepatocellular membrane and enhanced clearance of LDL-cholesterol (Kong et al. 2004). The actions of berberine have been shown to be independent of intracellular cholesterol levels and have no effect on SREBP promoter activity, indicating that SREBP are not involved in the mechanism of berberine-mediated LDLR up-regulation. Regulatory sequences involved in turnover rate and stability have been identified in the 3' untranslated region of the LDLR mRNA, and they appear to play an important role in the stabilization of LDLR mRNA by berberine (Kong et al. 2004). Another study identified two RNA binding proteins through which berberine may regulate LDLR mRNA stability (Li et al. 2009). Several studies also indicated that activation of the mitogen-activated protein kinase/extracellular-signal regulated kinase (MAPK/ERK) pathway might be a prerequisite event in berberine-mediated stabilization of the LDLR transcript (Kong et al. 2004; Abidi et al. 2005; Brusq et al. 2006). Kong et al. demonstrated these events in human hepatoma (HepG2) cells (using 7.5-15 μg/mL) and diet-induced hyperlipidemic hamsters (50 mg/kg berberine for 10 days). Additionally, a clinical trial in a small number of hyperlipidemic patients given oral berberine supplements (0.5 g berberine twice a day for 3 months) yielded promising results, with significant decreases in serum total cholesterol (-29%) and triglycerides (-35%) and LDL-cholesterol (-25%), but no change in cardioprotective high density lipoprotein-cholesterol levels (Kong et al. 2004).

Effects on triglycerides

While this mechanism explains the role of berberine in lowering serum cholesterol, it does little to account for the decline in triglycerides observed in human subjects. Hypertriglyceridemia contributes to a number of metabolic diseases, including cardiovascular disease, metabolic syndrome and type II diabetes (Cannon 2008). Studies by Brusq et al. (2006) have revealed a second mechanism by which berberine lowers lipids, particularly triglycerides. The authors showed that berberine activated AMP-activated protein kinase (AMPK), a kinase known to be involved in regulating energy balance in the cell (Hardie 2008). The two primary targets of AMPK are acetyl-CoA carboxylase (ACC) and HMG-CoA reductase (Carling et al. 1989). Berberine caused AMPK phosphorylation, a finding which was supported by several other studies (Lee et al. 2006; Turner et al. 2008), and the discovery that activation of AMPK by berberine was MAPK/ERK-dependent was confirmed (Kong et al. 2004; Brusq et al. 2006). The subsequent phosphorylation of ACC by AMPK slowed triglyceride synthesis and promoted the oxidation of fatty acids (Hardie and Pan 2002). Other studies reported decreases in plasma triglycerides of similar magnitudes in humans (Yin et al. 2008; Zhang et al. 2008).

A recent study examined the effect of a combination of berberine and simvastatin as cholesterol-lowering therapy in rodents and humans (Kong et al. 2008). The combination therapy decreased human and rat plasma LDL-cholesterol more effectively than either treatment alone, and boasts the advantage of requiring a low dose of both berberine and statin to achieve significant lipid lowering results.

ANTIOXIDANT EFFECTS

The growing list of therapeutic benefits that have become associated with berberine, including its anti-diabetic and cardioprotective properties, may be explained in part by its remarkably diverse antioxidant capabilities. Berberine has been shown to directly scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS) effectively in vitro. In biological systems, berberine appears to minimize the severity of oxidative stress by conserving the integrity of the innate antioxidant defense system and minimizing the extent of ROS generation.

Direct mechanism

The in vitro ROS/RNS scavenging abilities of berberine have been shown to be diverse, ranging from superoxide (O₂⁻) and nitric oxide (NO) quenching to limiting the formation of precarcinogenic reactive molecules such as peroxynitrite (ONO-O) and the hydroxyl radical (OH⁻). At low concentrations, berberine (50-100 μM) was found to inhibit DNA cleavage under pro-oxidative conditions namely due to its strong O₂⁻ scavenging abilities (Choi et al. 2001). Berberine has also been shown to be an effective peroxynitrite scavenger (Jung et al. 2009). The direct quenching of O₂⁻ and NO in vitro using colorimetric analysis was shown to be concentration dependant, although the efficacy of berberine (2-512 μg/mL) to directly scavenge ROS/RNS was found to be inferior to the well known antioxidant ascorbic acid (Shirwaikar et al. 2006). Using electron spin resonance spectroscopy, berberine (1 mM) was shown to actively scavenge the precarious OH· radical, a capability that is lost at lower concentrations (1-100 μM) (Choi et al. 2001).

Free iron in its oxidized ferrous form is extremely reactive under aerobic conditions, generating cytotoxic lipid peroxides via Fenton chemistry (Gutteridge 1995). Although berberine (50 μM-1 mM) has the ability to scavenge various ROS/RNS, its ability to chelate Fe(II) remains...


Berberine reduces lipid peroxidation in rat brain homogenate, a property accredited to its direct chelation of Fe(II) under experimental conditions (Shirwaikar et al. 2006). However, Jang and colleagues (2009) using slightly different analytical techniques, failed to observe similar ferrous chelation, a property that was attributed to berberine's inferior A ring positioning of the methylenedioxy functional group. Among structurally similar alkaloids such as berberine, it is through the D ring positioning of the methylenedioxy group is critical for facilitating optimal Fe(II) chelation (Jang et al. 2009). While berberine directly scavenges unstable species under experimentally simulated oxidative conditions, it is evident that berberine's antioxidant capabilities in biological systems go beyond the incidental interaction and inactivation of reactive molecular species.

**Indirect mechanisms**

1. **Berberine up-regulates endogenous antioxidant defense mechanisms**

In biological systems, berberine offers a complex array of antioxidant protection which has recently been brought to light. One mechanism whereby berberine regulates oxidative stress is through the conservation of non-enzymatic antioxidants, a phenomenon observed in vivo. Berberine (30 mg/kg body weight) was shown to prevent the decrease in the colonic supply of non-enzymatic antioxidants in a rat model of colon cancer. Colonic levels of glutathione, vitamin C and vitamin E were all conserved at relatively normal levels when berberine was co-administered with the carcinogen azoxymethane. Such maintenance was associated with reduced lipid peroxide generation, prevention of malignant morphological changes, and reduced cellular apoptosis. Significant protection was also achieved when affected animals were treated post exposure with berberine (30 mg/kg body weight), although the final protective outcomes were less obvious. The observed “sparring” of innate antioxidants may be a physiological consequence of berberine’s direct scavenging in vivo or a result of the elaboration of the endogenous antioxidant defense system altogether (Thirupurasundari et al. 2009). Nonetheless, a more complete investigation is warranted.

Besides maintaining the supply of endogenous antioxidant molecules, berberine has also been shown to regulate the activity of enzymes that catalyze the decomposition and removal of ROS from cell systems. These enzymes are integral for the maintenance of cellular redox as they are considered the first line of defense against oxidative stress. In cell culture studies, pre-treatment with berberine (25 μM) significantly increased superoxide dismutase (SOD) activity in lipopolysaccharide (LPS) stimulated human monocyte-derived macrophages and contributed to an overall reduction in intracellular superoxide (Sarna et al. 2010). Similar enhancement of SOD activity has also been observed in a rat model of Type I diabetes mellitus, SOD activity was restored to levels comparable to normoglycemic rats following the daily consumption of berberine (150-300 mg/kg). The increased activity of SOD in the diabetic rats was associated with reduced lipid peroxidation and the prevention of pathologically associated effects. Similar observations were made by Zhou et al. (2009). Daily administration of berberine (20 mg/kg) via stomach tube prevented the decline in serum SOD activity in rats experiencing a severe immune challenge (LPS administration during kidney ischemia reperfusion). Likewise, catalase and glutathione peroxidase activity were similarly restored, although these enzymes displayed a dose-dependent activation at both 10 and 20 mg/kg berberine. The restoration of enzymatic antioxidants in this particular model was associated with a reduction in serum superoxide and nitric oxide and an even more remarkable reduction in circulating OONO- (Yokozawa et al. 2004). Overall, berberine reduces the oxidative burden associated with pathologies such as cancer and diabetes, and conditions where critical immune challenge is present. The oxidative relief appears to be facilitated by the ability of berberine to conserve endogenous enzymatic antioxidants in vivo.

Besides maintaining the supply of endogenous enzymatic antioxidants in vivo or a result of the elaborate modulation of the endogenous antioxidant defense system altogether (Thirupurasundari et al. 2009). Nonetheless, a more complete investigation is warranted.

2. **Berberine suppresses endogenous ROS/RNS-generating Oxidases**

Besides the endogenous antioxidant defense system, another deciding factor that determines the redox status of a cell is the rate at which oxidative species are generated. Although ROS/RNS can be produced spontaneously, in biological systems, reactive molecules can also be accidentally or deliberately generated by specific oxidase enzymes. These oxidases are capable of generating ROS such as O₂⁻ and RNS such as NO with high efficiency and therefore play a major role in determining the cellular redox context. While enzymatic antioxidants such as SOD tend to be suppressed in various pathological conditions, enzymatic oxidases like the O₂⁻ generating reduced nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase tend to be activated. Therefore when investigating the antioxidant capacity of therapeutic agents in oxidative stress mediated disorders, it is equally important to consider their efficacy in modulating ROS/RNS generating systems.

A recent study demonstrated that berberine (25 μM) significantly inhibited NADPH oxidase mediated O₂⁻ production in LPS stimulated human monocyte-derived macrophages (Sarna et al. 2010). Berberine was found to regulate NADPH oxidase activity by selectively inhibiting gene expression of the enzyme's catalytic subunit, gp91phox (Sarna et al. 2010). Likewise, berberine (5 μM) inhibited the expression of inducible nitric oxide synthase (iNOS) in LPS treated murine macrophages, significantly reducing NO production in these cells (Jeong et al. 2009). Such inhibition of NO production was found to be mediated via an AMPK signaling pathway. Inhibition of ROS/RNS generating oxidase enzymes serves as one of the mechanisms through which berberine offers indirect antioxidant effect.

**BERBERINE AND ATHEROSCLEROSIS**

Hyperlipidemia is one of the major risk factors for cardiovascular disease. Apart from healthy life style, current pharmacotherapy is mainly achieved by lipid lowering medications. The majority of patients will be able to achieve target blood lipid levels on monotherapy or combined medications (Genest et al. 2009). However, some patients cannot tolerate medications such as statins and suffer from side effects (i.e. muscle pain and a decline in liver function). Berberine has now been shown to possess potent lipid lowering effects and it may be considered a future treatment for patients.
with hyperlipidemia.

Besides its lipid lowering properties, the diverse range of both direct and indirect antioxidant actions displayed by berberine attribute to its potential therapeutic application in the prevention of atherosclerosis. Atherosclerosis is characterized by thickening, hardening and loss of elasticity of the arterial wall, which can lead to fatal blockage of arteries. It is increasingly recognized that oxidative stress can elicit systemic inflammation, which in turn contributes to the development of cardiovascular disease. Atherosclerosis is a chronic inflammatory condition potentiated by the enhanced generation of ROS/RNS throughout the initiating and progressive stages of the disease (Madamanchi et al. 2005). One mechanism whereby berberine could retard the progression of atherosclerosis is through the inhibition of LDL oxidation. In vitro analysis of copper induced LDL oxidation demonstrated that berberine (25–100 μM) could effectively reduce such undesirable modifications in a concentration dependent manner (Hsieh et al. 2007).

Berberine has also been shown to attenuate oxidative stress in various vascular cells which could confer protection against the onset and development of atherosclerotic plaques. Berberine’s antioxidant properties may preserve the integrity of endothelial cells following exposure to oxidized LDL. Berberine has been shown to restore cell proliferation and viability, and subsequently prevent apoptosis in a concentration dependent manner in cultured endothelial cells. Such a protective effect was mediated by berberine’s (25-75 μM) ability to reduce endothelial oxidative stress and at a higher concentration (100 μM), completely abolish oxidative injury (Hsieh et al. 2007). NADPH oxidases, particularly the phagocytic isoform expressed in macrophages, are a key source of oxidative stress in human atherosclerotic plaques, contributing roughly 60% of the ROS/RNS generated in the atheroma (Sorensu et al. 2002; Guzik et al. 2006). Berberine has been shown to attenuate O2• production in stimulated macrophages. Such inhibition was mediated by berberine’s ability to reduce the expression of the catalytic subunit of NADPH oxidase as well as enhance SOD activity in activated macrophages (Sarma et al. 2010). In addition, berberine’s antioxidant capabilities may prevent the chronic release of inflammatory cytokines. It was shown to attenuate the release of TNF-α, IL-6 and MCP-1 in stimulated macrophages (Chen et al. 2008), a property associated with berberine’s suppression of ROS/RNS generation in these cells (Jeong et al. 2009).

FUTURE PERSPECTIVES

In conclusion, berberine is effective both in lipid-lowering and as an antioxidant. This compound has been shown to have potent lipid-lowering abilities both in animal models and in clinical trials of hyperlipidemic patients. Berberine has been well tolerated by virtually all subjects and has proven to be an effective compound for lowering cholesterol and triglycerides. Thus far, berberine has been shown to act via two complementary mechanisms distinct from the mechanisms which bring about a reduction in lipids. In light of these findings, we believe that berberine has great potential for use as an alternative or additional therapy for hyperlipidemia.

Berberine has displayed both a direct and indirect means of attenuating oxidative stress in various disease states. Future research should be directed towards deciphering the molecular mechanisms responsible for berberine’s ability to conserve intrinsic antioxidants and to regulate the many antioxidant enzymes. The therapeutic relevance of berberine in the prevention and management of atherosclerosis remains under investigation.

In many instances, enriched and standardized plant extracts of goldenseal, barberry or golden thread may be presented as alternative therapies for various physiological dysfunctions, especially in the age of rising healthcare costs. Placebo-controlled human clinical trials for these products should be encouraged and conducted and any adverse effects should be promptly reported. Otherwise, subscription to these products should be under the guidance of a primary healthcare provider.

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