Review Article

Physiological Effects of Berberine

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ABSTRACT

Berberine is a well-known plant alkaloid with a long history of medicinal use in Ayurvedic, Chinese, and South Asian traditional medicine. It can be found in the roots, rhizomes, and the bark of a number of plants. Plant extracts and decoctions involving berberine have demonstrated significant antimicrobial activity against a variety of organisms, intestinal parasite infections, and ocular trachoma infections. Positive action has been recorded against hypertension, tumors, inflammation, and HIV. It also has anti-protozoal, chloretic, cholagogue, cardiotonic, anti-cholinergic, anti-arrhythmic effects, and anti-platelet aggregation. This original review of berberine outlines its physiological effects.

Keywords: berberine, physiological effects

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Introduction

Berberine is a well-known plant alkaloid with a long history of use in Ayurvedic, Chinese, and South Asian traditional medicine. It is a component of plants such as *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Coptis or goldenthread), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), *Berberis aristata* (tree turmeric) (Berberis species), and *Arcangelisia flava*. It is found in roots, rhizomes, and bark of these plants. Berberine has several uses. For example, plant extracts and decoctions have significant antimicrobial activity against a variety of organisms such as bacteria, viruses, fungi, protozoans, helminthes, and chlamydia. Currently, the predominant clinical uses of berberine involve cases of bacterial diarrhea, intestinal parasite infections, and ocular trachoma infection.[1] It exhibits multiple pharmacological activities qualities such as being active against hypertension, tumors, bacteria, inflammation, and HIV. It also has anti-protozoal, chloretic, cholagogue, cardiotonic, anti-cholinergic, anti-arrhythmic effects, and anti-platelet aggregation. Some actions of berberine have been extensively studied and are addressed in the following sections.

Anti-diarrheal action

Berberine has been used for centuries in different parts of the world and is also used in the modern treatment of diarrhea. Its actions in this regard are manifested by its anti-cholinergic.[2] α_2-adrenoreceptor agonistic[3], anti-secretory[4] and/or antimicrobial effects.[5,6] In in vivo study by Swabb et al (1981), berberine reduced the intestinal transit time of the secretion of water and electrolytes induced by cholera toxin.[7] It has also been shown to directly inhibit some *V. cholera* and *E. coli* enterotoxin[8], reduce smooth muscle contraction and intestinal motility[6], and delay intestinal transit time in humans. In the case of *E. coli, in vitro* research indicated that berberine sulfate is able to inhibit bacterial

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adherence to mucosal or epithelial surfaces, the first step in the infective process. This may be a result of its inhibitory effect on fimbrial structure formation on the surface of the treated bacteria.[9] In animal study, berberine significantly inhibited both the diarrhea induced by castor oil and that induced by $BaCl_2$ at doses higher than 25 mg/kg given orally, but it did not inhibit diarrhea induced by pilocarpine or serotonin even at 250 mg/kg. Berberine inhibited acetylcholine (Ach) - or Ba^{2+}-induced contraction of the ileum and colon at the concentration of about 10^{-5} g/mL.[10]

Anti-malarial action

Berberine has been used for the treatment of malaria. In Vietnam, it was collected from 14 medicinal plants and used in traditional treatment of the disease. Twenty-four extracts from these plants were found to have anti-plasmodial effects inhibiting the growth of the chloroquine-resistant *P. falciparum* strain FCR-3 with EC_{50} values of less than 10 μg/mL. The methanol extract of *Coscinium fenestratum* was found to have the strongest anti-plasmodial effect with EC_{50} value of 0.5 μg/mL. Activity-guided fractionation led to the identification of berberine as the major activity component.[11] Sriwilaijareon et al (2002) examined telomerase activity in synchronized *P. falciparum* during its erythrocytic cycle using the telomerase repeat amplification protocol (TRAP).[12] They reported that berberine extract inhibited telomerase activity in a dose-dependent manner over a range of 30-300 μM. It indicated that *P. falciparum* telomerase might be a potential target for future malaria chemotherapy.

Anti-tumor action

Berberine possesses anti-tumor properties as evidenced by the inhibition of cyclooxygenase-2 (COX-2) transcription and N-acetyltransferase (NAT) activity in colon and bladder cancer cell lines.[13,14] Its action is transient but markedly inhibits the growth of mouse sarcoma cells in culture. Wang et al (2002) reported the anti-neoplastic action of berberine in rats.[15] The alkaloid inhibited and decreased aryamine NAT activity, levels of mRNA NAT1, and 2-aminofluorence-DNA (AF-DNA) adduct formation in human brain tumor cell lines (G95/VGH and GBM 8401) in a dose-dependent manner. Results showed that berberine apparently decreased the values of Km and Vmax of NAT of both cells. The results also indicated that berberine is a non-competitive inhibitor. In human leukemia cells, the NAT activity and AF-DNA adduct formation were inhibited by berberine in a dose-dependent manner, the higher the concentration of berberine, the higher the inhibition of NAT activity and AF-DNA adduct. It was also shown that berberine inhibits the viability and NAT activity in human tumor cells line and human bladder tumor cells in dose-dependent manner, that is the higher the concentration of berberine, the higher the inhibition of NAT activity. The apparent values of Km and Vmax of NAT from colon tumor cells were also inhibited by berberine in cytosols and in intact cells. Studies illustrated that berberine did not affect human colon tumor cell and NAT activity in human bladder tumor cell.[13,14,16] Moreover, it has been shown to have an anti-cachectic effect on esophageal cancer. Its effect is associated with the ability to down-regulate tumor IL-6 production.[17] Lin et al (2008) studied the viability of rat C6 and human U-87 glioma cells after treatment with As_2O_3 or berberine.[18] They found that both significantly decreased the activation of PCK α and ε and led to actin cytoskeleton rearrangements. The levels of two downstream transcription factors, myc and jun, and MTI-MMP and MMP-2 were also significantly reduced. These results indicated that upon co-treatment of glioma cells with As_2O_3 and berberine, cancer cell metastasis can be significantly inhibited, most likely by blocking the PKC-mediated signaling pathway involved in cancer cell migration. This has potential in the development of new chemotherapeutic approaches in the treatment of malignant glioma and cancer in general.

In in vitro study, the continuous exposure of HepG2 cells to various concentrations (1-50 μM) of berberine resulted in growth inhibition in a dose-dependent manner.[19] The viability of berberine-treated HepG2 cells was greater than 90% in all treated groups. Flow

cytometric analysis of berberine-treated HepG2 cells showed that the S phase fraction was significantly reduced. The levels of glucocorticoid receptors (GR) in berberine-treated HepG2 cells were higher than those in vehicle (DMSO)-treated cells. In addition, berberine inhibited the secretion of alpha-fetoprotein by HepG2 cells suggesting that berberine-induced cell growth arrest was partially reversible in HepG2 cells. Cameron et al (2008) investigated the effect of berberine on *PCSK9* expression in HepG2 cells.[20] They found that berberine decreases *PCSK9* mRNA and protein levels in a time- and dose-dependent manner. This was not due to increase degradation of *PCSK9* mRNA but most likely due to a decreased transcription of the *PCSK9* gene. This suggested that berberine may be a useful supplement to statin treatment in lipid lowering drugs, due to its effect on *PCSK9* mRNA and protein levels.

Cardiovascular action

Both clinical trials and animal research have indicated that the administration of berberine prevents ischemia-induced ventricular tachyarrhythmia. It stimulates cardiac contractility and lowers peripheral vascular resistance and blood pressure.[21,22] An animal study by Wang et al (1994) indicated that berberine may suppress the delayed after-depolarization in the ventricular muscle.[23] Some cardiovascular effects of berberine are attributed to the blockage of K^+ channels (delayed rectifier and K^+ (ATP)) and the stimulation of Na^+-Ca^{2+} exchange. Berberine has been shown to prolong the duration of ventricular action potential.[24] In addition to the several effects on other parameters of cardiac performance, berberine may have vasodilating and antihypertensive effects attributable to the potential of Ach.[21]

Anti-inflammatory and antihepatotoxic actions

Berberine is an effective anti-inflammatory agent. *In vitro* studies utilizing human cell lines demonstrated that it inhibits activator protein 1 (AP-1), a key transcription factor in inflammation and carcinogenesis.[14] By using human peripheral lymphocytes, berberine exerts a significant inhibitory effect on lymphocyte transformation. It was suggested that its anti-inflammatory action may be due to the inhibition of DNA synthesis in activated lymphocytes.[25] In a study on platelet activation in response to tissue injury, berberine was shown to have a direct effect on several aspects of the inflammatory process. It exhibits a dose-dependent inhibition of arachidonic acid release from the cell membrane phospholipids, reduces thromboxan A2 from platelet[26], and decreases thrombus formation.[27] Recently, Janbaz and Gilani (2000) demonstrated the preventive effects of berberine (oral dose of 4 mg/kg) against acetaminophen and carbon tetrachloride (CCl_4) -induced hepatotoxicity by which it inhibited the activities of microsomal drug metabolizing enzymes, CYPs.[28] Surprisingly, it was believed that berberine has a selective curative effect related to acetaminophen but not CCl_4 due to its antioxidative role. This was further supported by reports that the acetaminophen toxicity is chiefly due to the oxidative stress and is effectively improved by antioxidants.[29] Berberine is also an effective antioxidant. Castro et al (1974) and Nelson et al (1980) reported that the inhibitors of cytochrome P450s (CYPs) can impair the bio-activation of CCl_4 into its respective reactive species and provide protection against the prevailing hepatocellular damage.[30,31]

Hwang et al (2002) studied the mechanism of the inhibitory effects of berberine on the tert-butyl hydroperoxide (t-BHP)-induced cytotoxicity and lipid peroxidation in rat's livers. They found that berberine expressed an antioxidative property by its capacity for quenching the free radicals of 1,1-diphenyl-2-picrylhydrazyl (DPPH).[32] *In vitro* studies utilizing rat's primary hepatocytes demonstrated that berberine at the concentrations of 0.01 - 1.0 mM significantly decreased the leakage of lactate dehydrogenase (LDH) and alanine aminotransferase (ALT), and the formation of malondialdehyde (MDA) after treatment with t-BHP (1.5 mM) for 30 minutes. In addition, berberine attenuates the t-BHP-induced depletion of liver glutathione (GSH) and inhibits the t-BHP-induced genotoxicity in hepatocytes. *In vitro* studies showed that intra-peritoneal pre-treatment

with berberine at dose of 0.5 and 5 mg/kg for 5 days before a single dose of t-BHP (0.1 mmol/kg) significantly prevents the elevation of the liver transaminases and reduced oxidative stress in the liver. Therefore, berberine inhibits the hepatotoxicity induced by t-BHP through its antioxidative potential suggesting that it may play a chemo-preventive role by reducing oxidative stress in living systems. In addition, it is claimed that beberine could inhibit CYP2E1 mediated oxidation of *p*-nitrophenol *in vitro*.[33] Zhao et al (2007) reported that oral administration of berberine (50 mg/kg) inhibited the hepatocyte proliferation and inducible nitrix oxide synthase (iNOS) expression, decreased CYP450 content, and inhibited activities of CYP2E1 and CYP1A2 in diethylnitrosamine (DEN)–plus-phenobarbital (PB)–treated rat *in vivo*.[34] Berberine (10, 50 and 100 μM) was also found to inhibit the activities of CYP2E1 and CYP1A2 in microsomal isolated from DEN-plus-PB-treated rats *in vitro* suggesting that the anti-hepatocarcinogenetic potential of berberine might be due to the inhibition of oxidative metabolic activities of CYP2E1 and CYP1A2 and the decrease of nitric oxide (NO) production in rats.

Other activities

Kong et al (2004) found that berberine upregulates low-density lipoprotein receptor (LDLR) expression in human hepatocytes through an extracellular signal-regulated kinase (ERK)-dependent mechanism.[35] These researchers found that berberine significantly lowered blood cholesterol, triglyceride and LDL cholesterol (LDL-C) in patients with hyperlipidemia and elevated LDLR expression in the hepatitis B virus (HBV) full genome-infected human hepatocytes. In addition, berberine reduced blood lipid, cholesterol, triglyceride and LDL-C in the hyperlipidemic hepatitis C and liver cirrhosis. The study suggested that berberine could be an ideal drug to control lipid metabolism alone or in combination for the patients with hyperlipidemic hepatitis or liver cirrhosis.[36] Moreover, it was shown that berberine induced c-Jun binding to LDLR promoter in berberine-induced LDLR transcription. Also, it was demonstrated that berberine increases transcriptional activity of LDLR promoter and this involves JNK pathway.[37]

The suppressive effects of berberine on receptor activator of nuclear factor κB (NF-κB) ligand (RANKL)-induced formation and survivals of osteoclast were studied. Berberine inhibited RANKL-mediated osteoclast formation and survival through the suppression of NF-κB and Akt pathways.[38]

In addition, berberine was found to stimulate glucose uptake in a time- and dose-dependent manner. Investigation showed that it strongly promotes the phosphorylation of AMPK and p38 MAPK. These suggested that berberine circumvents insulin signaling pathways and stimulates glucose uptake through the AMP-AMPK-p38 MAPK pathway.[39] Zhou et al (2007) showed that berberine stimulated glucose uptake in 3T3-L1 adipocytes in a dose- and time-dependent way.[40] Berberine-stimulated glucose uptake was additive to that of insulin in 3T3-L1 adipocytes. In addition, berberine increased adenosine monophosphate-activated protein kinase and acetyl-coenzyme A carboxylase phosphor-ylation. These findings indicated that berberine increases glucose uptake through a mechanism distinct from insulin, and stimulated adenosine monophosphate-activated protein kinase seems to be involved in the metabolic effect of berberine.

Conclusion

Berberine has been found in the roots, rhizomes, and bark of a number of plants and it has been demonstrated to have significant physiological effects. These include antimicrobial activities against a variety of organisms, intestinal parasite infections, and ocular trachoma infections. It has been reported to act against hypertension, inflammation, HIV, tumors, and have antiprotozoal, chloretic, cholagogue, cardiotonic, anticholinergic, antiarrhythmic effects, and antiplatelet aggregation. In addition, berberine has been shown to affect blood lipid, cholesterol, triglyceride, LDL-C and glucose uptake.

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