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REVIEW ARTICLE

Pharmacological and Therapeutic Effects of *Berberis vulgaris* and its Active Constituent, Berberine

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Barberry (*Berberis vulgaris* L. family Berberidaceae) is well known in Iran and various parts of this plant including its root, bark, leaf and fruit have been used as folk medicine. The two decades of research has demonstrated different pharmacological and therapeutic effects of *B. vulgaris* and its isoquinoline alkaloids (particularly berberine). Studies carried out on the chemical composition of the plant show that the most important constituents of this plant are isoquinoline alkaloids such as berberine, berbamine and palmatine. Berberine represents one of the most studied among the naturally occurring protoberberine alkaloids. In addition to *B. vulgaris* (barberry), berberine is present in many other plants and is used for the treatment of different diseases. This article reviews the traditional uses and pharmacological effects of total extract and the most active ingredient of *B. vulgaris* (berberine). Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: barberry; *Berberis vulgaris*; berberine.

INTRODUCTION

Barberry (*Berberis vulgaris* L. family Berberidaceae) grows in Asia and Europe; the plant is well known in Iran and has been used extensively as a medicinal plant in traditional medicine. The fruits of the plant have been also used as a food additive. The plant is a shrub, 1–3 m tall, spiny, with yellow wood and obovate leaves, bearing pendulous yellow flowers succeeded by oblong red fruits (barberry) (Shamsa *et al.*, 1999).

The various parts of *B. vulgaris* including its root, bark, leaf and fruit have been used as folk medicine for a long time in Iran and other countries (Table 1). In pharmacological research, there is some evidence for different effects of the *B. vulgaris* (Table 2) or isoquinoline alkaloids of the genus *Berberis* (particularly berberine) (Table 3). There are also some clinical trials of the therapeutic effects of this plant or berberine (Table 4).

Studies carried out on the chemical composition of the extracts show that the alkaloid constituents with an isoquinolinic nucleus such as berberine, berbamine and palmatine (Fig. 1, Table 5) are important compounds of this plant (Ivanovska and Philipov, 1996). In a quantitative HPLC analysis of the main alkaloids in the roots, barks and stems of *B. vulgaris*, the amounts of berberine and berbamine were 1.24% and 2.5%, respectively. Although berberine is the most important alkaloid that is generally claimed to be responsible for their beneficial effects and numerous studies have been conducted so far (Küpeli *et al.*, 2002) but it is pointed out that other alkaloids also have some roles in the effects of the plant (Yeşilada and Küpeli, 2002).

Berberine, an isoquinoline plant alkaloid, belongs to the structural class of protoberberines. Berberine represents one of the most studied among the naturally occurring protoberberine alkaloids (Mazzini *et al.*, 2003). In addition to *B. vulgaris* (barberry), berberine is present in many other plants including *Hydrastis canadensis* (goldenseal) (Ranunculaceae), *Coptis chinensis* (Coptis or goldenthread) (Ranunculaceae), *Arcangelisia flava* (Menispermaceae), *B. aquifolium* (Oregon grape) and *B. aristata* (tree turmeric) (Wang *et al.*, 2004a; Peng *et al.*, 2004). Berberine is used for the treatment of different diseases (Table 3). This article reviews the pharmacological effects of the total extract and the most active ingredient of *B. vulgaris* (berberine).

CARDIOVASCULAR EFFECTS

In traditional medicine, *B. vulgaris* has been used in various heart diseases including hypertension and arrhythmia (Fatehi-Hassanabad *et al.*, 2005; DerMaderosian, 2001). Several pharmacological studies have indicated the cardiovascular effects of berberine and *B. vulgaris* including preventing ischemia induced ventricular tachyarrhythmia, improving cardiac contractility and lowering peripheral vascular resistance and blood pressure (Chun *et al.*, 1979; Marin-Neto *et al.*, 1988).

Vasorelexant and hypotensive effect. One study on the aqueous extract of *B. vulgaris* showed that administration of the extract (0.05–1 mg/100 g body weight of rat) significantly reduced the mean arterial blood pressure and heart rate dose dependently in rats. This result

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Table 1. The traditional uses of *Berberis vulgaris* (NAPALERT = Natural Products Alert Database)

System	Effect	Part of plant	Preparation	Country
Cardiovascular	Antiedema	Dried leaf	Infusion	Iran
	Antihypertensive	Stem bark	Decoction	France
	In varicose veins		Decoction (external)	Iran
Blood	Blood rectifier	Dried root cortex	Decoction	Iran
Gastrointestinal	Choleretic	Dried entire plant	Infusion	Iran
	Cholagogue	Root	Fluid extract	France
	Laxative	Dried root	Decoction	Iran
		Dried entire plant	Infusion	Iran
		Dried root – dried root bark	Decoction	Iran
		Fruit		Turkey
	Stomachic	Fruit	Infusion	Turkey
	Beverage in severe diarrhea	Dried fruit – dried leaf	H_2O extract-infusion	Iran
	Diarrhea	Root	Root	India
	Hepatic malfunctions	Dried fruit	H_2O extract	Iran
	Bowel movement disorders associated with hepatic malfunctions	Dried root bark + stem bark	Decoction	Iran
	Gall bladder and liver disorders	Dried root	Root	Bulgaria
	Hepatitis	Dried root bark	Decoction	Iran
	Intestinal ulcers	Root	Root	India
	Indigestion associated with hepatic disorders or loss of appetite.	Dried root bark	Decoction	Iran
	In hemorrhoids		Decoction	Iran
Endocrine	Painful menstruation	Fruit	Hot H_2O extract	Argentina
		Dried root	Root	Bulgaria
	Inhibit pregnancy	Root	Hot H_2O extract	Afghanistan
	Promote fertility-male	Root	Hot H_2O extract	Afghanistan
	Uterine bleeding	Root	Fluid extract	France
Immune system	Antiinflammatory	Dried root	Root	Bulgaria
	Rheumatoid arthritis	Dried root bark + stem bark	Decoction (external)	Iran
	Antirheumatic	Flowers	Decoction	China
	Gout		Decoction	Iran
Organisms	Antimicrobial	Dried root	Root	Bulgaria
	Beverage in typhus	Dried fruit	H_2O extract	Iran
	In malaria		Decoction	Iran
Central nervous system	Beverage to reduce fever	Dried fruit	H_2O extract	Iran
	Antipyretic	Dried root cortex	Decoction	Iran
	Sedative	Dried root	Root	Bulgaria
Respiratory	Whooping cough	Fruit	Decoction	Turkey
	Gargle to reduce common cold symptoms	Dried leaf	Infusion	Iran
	Blood vomiting due to lung disorders	Root	Root	India
Skin	Irrigate wounds or ulcers	Dried leaf	Infusion	Iran
	In scorbutic patients	Dried leaf	Infusion	Iran
	Chewed by scorbutic patients to harden gums	Leaf	External	Iran
	Disinfectant	Dried root cortex	Decoction (external)	
Renal	Renal or urinary calculi	Dried part not specified	Hot H_2O extract	India
	Diuretic	Dried root	Decoction	Iran
	Kidney inflammation	Dried root	Root	Bulgaria
	Nephritis	Dried root bark	Decoction	Iran
Other	Astringent	Dried fruit	H_2O extract	Italy
	Gargle, cooling effect	Dried fruit	Hot H_2O extract	USA
	Tonic effect	Dried root	Decoction	Iran

suggests a central effect since both blood pressure and heart rate were decreased in a parallel pattern. In pathological conditions, such as hypertension, an extract of 1 g dried barberry per day for at least 5 consecutive days is recommended (personal communication with some herbal medicine specialists in Iran); these results concerning the efficacy of the extract obtained from *in vivo* experiments are comparable to dosages recommended in folk medicine (Fatehi-Hassanabad *et al.*, 2005). Another *in vitro* study showed that the aqueous

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Table 2. The pharmacological effects of *Berberis vulgaris*

System	Effect	Part of plant	preparation	Reference
Cardiovascular	Hypotensive activity	Dried root	Alkaloid fraction	NAPALERT
		Dried fruit	Aqueous extract	Fatehi-Hassanabad *et al.*, 2005
Gastrointestinal	Gastric secretory stimulation	Root	Ethanol–H_2O (67%) extract	NAPALERT
	Choleretic activity in rat	Dried root		NAPALERT
	Choleretic activity	Stem bark	Total alkaloids	NAPALERT
	Increases tone of the digestive tract and gives rise to increased and irregular peristalsis	Dried root		NAPALERT
	Anticholinergic activity in guinea pig ileum	Dried fruit	Decoction	NAPALERT
Endocrine	Menstruation induction effect in guinea pig	Stem	Ethanol (95%) extract	NAPALERT
	Uterine stimulant effect in cat, rabbit and guinea-pig	Leaf	Ethanol-acetone (50%) extract	NAPALERT
Immune system	Antibody formation suppression in mouse	Dried root	Alkaloid fraction	NAPALERT
	Antiinflammatory activity	Root	Alkaloid fraction	Ivanovska and Philipov, 1996
		Root	Ethanol (100%) extract	Ivanovska and Philipov, 1996
	Complement alternative pathway inhibition		Alkaloid fraction and ethanol (95%) extract	NAPALERT
	Delayed type cutaneous hypersensitivity inhibition		Alkaloid fraction	NAPALERT
Organisms	Antibacterial – *Providencia stuartii*	Dried bark	Tincture	NAPALERT
	Antibacterial – *Sarcina flava*	Dried bark	Tincture	NAPALERT
	Antibacterial – *Serratia* species	Dried bark	Tincture	NAPALERT
	Antibacterial – *Klebsiella pneumoniae*	Dried entire plant	Methanol extract	NAPALERT
	Antibacterial – *Staphylococcus aureus*	Dried entire plant	Methanol extract	NAPALERT
		Root	Fluid extract	NAPALERT
	Antibacterial – *Mycobacterium phlei*	Dried entire plant	Methanol extract	NAPALERT
	Antifungal – *Candida albicans*	Dried entire plant	Methanol extract	NAPALERT
	Escherichia coli	Root	Fluid extract	NAPALERT
Central nervous system	Antipyretic activity in rat	Dried bark	Alkaloid fraction	NAPALERT
		Dried fruit	Ethanol (95%) extract	NAPALERT
	Narcotic antagonist activity	Dried root		NAPALERT
	Sedative	Fruit		Fatehi-Hassanabad *et al.*, 2005
Renal	Diuretic activity in rat	Dried bark	Alkaloid fraction	NAPALERT
Other	Toxicity assessment in mouse – LD_{50} = 520.0 mg/kg	Dried root	Alkaloid fraction	NAPALERT
	Toxicity assessment in mouse – LD_{50} = 2.6 ± 0.22 g/kg b.w.			Peychev, 2005

extract of this plant has a relaxant effect on rings of descending aorta and isolated perfused mesenteric artery in a mainly endothelial-independent manner (Fatehi-Hassanabad *et al.*, 2005). In another study, a long term hypotensive effect caused by the intravenous injection of 10% infusion of the plant has been considered as evidence of its direct myotropic effect (Peychev, 2005).

In vivo and *in vitro* experiments have also shown blood pressure lowering (Chun *et al.*, 1979) and vasorelaxatory (Chiou *et al.*, 1991) effects of berberine. Nevertheless, the vascular sites for the hypotensive activity of berberine are not clear. It seems that berberine acts on both endothelium and the underlying vascular smooth muscle to induce vasorelaxation via multiple cellular mechanisms (Ko *et al.*, 2000). Wong showed that aortic relaxation induced by berberine below 1×10^{-6} M was solely endothelium dependent. Higher concentrations (above 1×10^{-6} M berberine), however, induced aortic relaxation irrespective of the presence of intact endothelium (Wong, 1998). The mechanisms suggested for the vasorelaxation effect of berberine include an α_1-adrenoceptor antagonistic action in rat and rabbit aorta (Olmez and Ilhan, 1992), ACE-inhibitory activity and directly release of NO/cGMP from rat aortic rings (Kang *et al.*, 2003), the activation of tetrapentylammonium, 4-aminopyridine and Ba^{2+}-sensitive K^+ channels, the inhibition of intracellular Ca^{2+} release from caffeine-sensitive pools, blocking of L-type calcium channels (Kang *et al.*, 2003; Chiou *et al.*, 1998; Ko *et al.*, 2000; Xu *et al.*, 1997) and the potentiation of acetylcholine (Chun *et al.*, 1979).

Inducing penile erection. In male New Zealand rabbits, the intercavernosal injection of berberine possesses a relaxant effect on the rabbit corpus cavernosum tissue which is attributable to both endothelial-dependent and -independent properties (Chiou *et al.*, 1998). The authors are of the opinion that berberine has the

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Table 3. The pharmacological effects of berberine

System	Effect	Reference
Cardiovascular	Hypotensive,	Birdsall and Kelly, 1997; Huang *et al.*, 1991b; Wang *et al.*, 1993
	Vasorelaxation	Chiou *et al.*, 1991; Ko *et al.*, 2000
	ACE-inhibitory activity and release of NO/cGMP from rat aorta	Kang *et al.*, 2003
	Enhancement of eNOS mRNA expression in rat penis	Tan *et al.*, 2005
	Inhibition of PDE5 mRNA expression,	Tan *et al.*, 2004
	Preventing the ventricular hypertrophy	Yang *et al.*, 2004
	Improvement of neointima formation after balloon injury	Lee *et al.*, 2006
	Alleviating ischemic/reperfusion injury	Zheng *et al.*, 2003
	Antiarrhythmic	Wang and Zheng, 1997; Huang *et al.*, 1991b
	Cholesterol lowering activity via upregulation of low-density lipoprotein (LDL) receptor expression	Kong *et al.*, 2004; Abidi *et al.*, 2005
	Inhibition of vascular smooth muscle cell (VSMC) proliferation	Lee *et al.*, 2006; Tanabe *et al.*, 2005
Blood	Antiplatelet effect via inhibition of thromboxane A2 synthesis	Huang *et al.*, 2002
	Antiplatelet effect via platel *et al.* pha 2 adrenoceptor	Hui *et al.*, 1991
Gastrointestinal	Anticholinergic	Tsai and Ochillo, 1991
	Treatment of diarrhea	Dutta *et al.*, 1972; Sack and Froehlich, 1982
	Bacterial enteritis	Rabbani *et al.*, 1987
	Hepatoprotection	Hsiang *et al.*, 2005
	Choleretic action	Hobara and Watanabe, 1984
	Inhibition of CYP3A4 in the liver and/or small intestine	Wu *et al.*, 2005; Xin *et al.*, 2002
Endocrine	Antihyperglycemic agent	Pan *et al.*, 2003; Yin *et al.*, 2002
	Antiosteoporosis	Li *et al.*, 1999
Immune system	Immuno-stimulating	Birdsall and Kelly, 1997
	Blocking the induction of edema on mouse ear by 12-Otetradecanoylphorbol-13-acetate (TPA)	Yasukawa *et al.*, 1991
	Inhibition of cyclooxygenase-2 (COX-2) transcriptional activity through the regulation of activator protein 1 (AP-1) transcription factor	Fukuda *et al.*, 1999
	Immunomodulation of adjuvant-induced arthritis	Ivanovska and Philipov, 1996
Organisms	Anti-HIVactivities	Vlietinck *et al.*, 1998
	E. histolytica, G. lamblia, T. vaginalis	Kaneda *et al.*, 1991
	H. pylori	Mahady *et al.*, 2003
	L. donovani	Ghosh *et al.*, 1985
	S. aureus	Freile *et al.*, 2003
	C. albicans	Freile *et al.*, 2003
Central nervous system	Antinociceptive activity	Küpeli *et al.*, 2002
	Anxiolytic activity	Peng *et al.*, 2004
	Improvement of scopolamine-induced amnesia	Peng *et al.*, 1997
	Inhibition of MAO-A	Kong *et al.*, 2001
	Inhibition of MAO-B	Castillo *et al.*, 2005
	Inhibition of acetylcholinesterase	Kim *et al.*, 2004; Whiteley and Daya, 1995
	Inhibition of tyrosine hydroxylase	Shin *et al.*, 2000
	Inhibition of tryptophan hydroxylase	Lee *et al.*, 2001
	Neuroprotective effect	Wang *et al.*, 2004a
Skin	Increasing of skin permeation of polar drugs	Namba *et al.*, 1995
Other	Inhibition of DNA and protein synthesis, anti-cancer effect	Sethi, 1983; Kettmann *et al.*, 2004
	Cytotoxicity against HeLa (uterus carcinoma), SVKO3 (ovary carcinoma), Hep-2 (larynx carcinoma), human and rat malignant brain tumors and two types of esophageal cancer cell lines (YES-3 and YES-4)	Orfila *et al.*, 2000; Zhang *et al.*, 1990; Iizuka *et al.*, 2000b
	Displacing of bilirubin from albumin	Chan, 1993
	Protection against carcinogens	Chung *et al.*, 1999; Lin *et al.*, 1999b; Chung *et al.*, 2000; Lin *et al.*, 2005
	Inhibition of cyclophosphamide-induced bladder oedema and hemorrhage in rat.	Xu and Malave, 2001
	Reduction of renal toxicity of cyclosporine A	Ni *et al.*, 2003
	Lipogenesis in the hamster sebaceous glands	Seki and Morohashi, 1993

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Table 4. The clinical trials of therapeutic effects of *Berberis vulgaris* and berberine

Disease	Number of patients/ dose of treatment	Probable mechanism(s)	Reference
Dyslipidemias	40	Increase in hepatic LDLR mRNA and hepatic LDLR protein	Cicero Arrigo, 2007; Kong *et al.*, 2004
Congestive heart failure	79/ berberine 1.2 to 2.0 g/day (added to other drugs)	Modulating the sympathetic nervous activity, increasing the concentration of high energy phosphate and moderate [Ca2+]i increase	Zeng *et al.*, 2003; Zeng and Li, 2001
Platelet aggregation		Inhibitory effects on arachidonic acid metabolism and calcium influx, partial agonist activity on platelet α2-adrenoceptors	Huang *et al.*, 2002; Wu and Liu, 1995; Huang *et al.*, 1991a; Hui *et al.*, 1991; Huang *et al.*, 2002
Chloroquine-resistant malaria	82	inhibitory activity against sortase A (SrtA) and sortase B	Sheng *et al.*, 1997
Vibrio cholerae and Escherichia coli diarrhrea	Berberine 200 mg	Antimicrobial activity, decrease of mast cell-mediated chloride secretion, delaying the small intestinal transit time, direct anti-secretory action	Rabbani, 1996; Taylor and Baird, 1993; Yuan *et al.*, 1994
Chlamydia trachomatis infection	51/ berberine as eye drop 6/ berberine 300 mg	Berberine chloride has no direct anti-chlamydial properties, but it seemed to cure the infection by stimulating some protective mechanism in the host.	Anonymous, 2000
Pharmacokinetic interaction with cyclosporine A		Inhibition of CYP3A4, increase in emptying time of stomach and small	Wu and Liu, 2005; Xin *et al.*, 2002, 2006

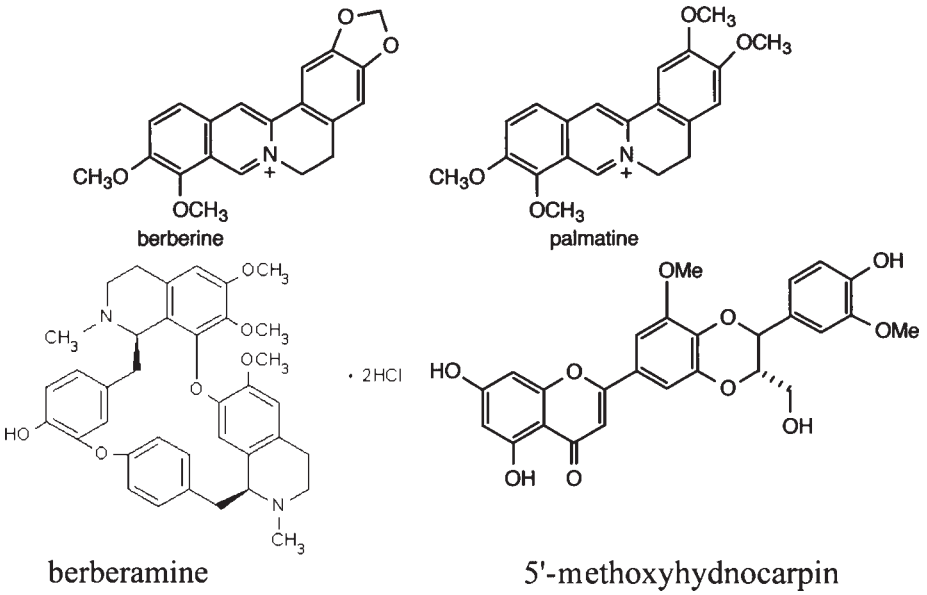

Figure 1. Structure of some active constituents of *Berberis vulgaris* (Stermitz *et al.*, 2000).

potential to be used as a drug for intravenous injection therapy. It has been pointed out that while papaverine appears to be more effective than berberine in inducing penile erection, the duration of tumescence caused by berberine is considerably longer. Also, berberine causes only a transient hypotensive action (Drewesa *et al.*, 2003). In a mechanistic aspect, the enhancement of eNOS mRNA expression in rat penis (Tan *et al.*, 2005) and inhibition of PDE5 mRNA expression, (especially PDE5A2) (Tan *et al.*, 2004), have been investigated for this effect of berberine.

Inotropic and protective effects. Berberine is used in the Orient for the treatment of congestive heart failure (CHF) (Zeng *et al.*, 2003). Some studies have shown berberine exerts protective effects against hypertrophy (Yang *et al.*, 2004; Hong *et al.*, 2002, 2003), ischemia reperfusion injury of the heart and severe congestive heart failure (Zeng *et al.*, 2003; Zhou *et al.*, 2001). For example, one study has shown that berberine can improve the damaged heart function of CHF rats caused by aortic binding and inhibit the development of cardiac hypertrophy (Hong *et al.*, 2002). In a clinical study,

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Table 5. Chemical compounds of *Berberis vulgaris* (NAPALERT)

Compound	Type	Part of plant
Acanthine	Isoquinoline alkaloid	Root
		Bark
		Root bark
		Stem bark
		Shoots
		Leaf
Aesculetin	Coumarin	Fruit
Ascorbic acid	Vitamin	Fruit
		Leaf
Bargustanine	Isoquinoline alkaloid	Root
Berbamine	Isoquinoline alkaloid	Bark
		Root
		Stem bark
Berberrubine	Isoquinoline alkaloid	Root
Berberine	Isoquinoline alkaloid	Root
		Root bark
		Bark
		Stem bark
		Root wood
		Flowers
		Stem
		Fruit
		Shoots
Berberrubine	Isoquinoline alkaloid	Bark
Berlambine	Isoquinoline alkaloid	Root
Bervulcine	Isoquinoline alkaloid	
Caffeic acid	Phenylpropanoid	Fruit
Carotene, beta:	Carotenoid	Fruit
Chlorogenic acid	Phenylpropanoid	Fruit
Chrysanthemin	Flavonoid	Fruit
Columbamine	Isoquinoline alkaloid	Root
		Bark
		Stem bark
Delphinidin-3-o-beta-d-glucoside	Flavonoid	Leaf
Glucan, alpha:	Carbohydrate	Leaf
Hyperoside	Flavonol	Fruit
		Leaf
Jatrorrhizine	Isoquinoline alkaloid	Root
		Root bark
		Bark
		Stem bark
Lambertine	Isoquinoline alkaloid	Root
Magnoflorine	Isoquinoline alkaloid	Root bark
		Root
		Stem bark
Malic acid	Alkane to c4	Fruit
Palmatine	Isoquinoline alkaloid	Root
		Bark
		Root bark
		Fruit
Pectin	Carbohydrate	Fruit
Pelargonin	Flavonoid	Fruit
Petunidin-3-o-beta-d-glucoside	Flavonoid	Fruit
Polysaccharide	Carbohydrate	Leaf
Quercitrin	Flavonol	Leaf
Sucrose	Carbohydrate	Fruit
Tannin	Tannin	Fruit
Thalicmidine	Isoquinoline alkaloid	Leaf
Tocopherol,alpha:	Oxygen heterocycle	Leaf
Ursolic acid	Triterpene	Fruit
Vitamin K	Vitamin	Leaf
Vulvracine	Alkaloid-misc	
Xylan,beta	Carbohydrate	Leaf

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berberine decreased the frequency and complexity of ventricular premature complexes (VPCs) and increased the left ventricular (LV) ejection fraction (EF) in patients with CHF (Zeng and Li, 2001). Modulating the sympathetic nervous activity (Hong *et al.*, 2003), increasing the concentration of high energy phosphate in the failure heart (Zhou *et al.*, 2002) and moderating the $[Ca^{2+}]i$ increase via Ca^{2+} influx and intracellular Ca^{2+} release (Li and Wang, 1997) are mechanisms that have been suggested for these effects of berberine. In total, the significant vasodilator effect of berberine, coupled with its potent positive inotropic effect, make this an ideal agent to be considered in congestive heart failure.

Antiplatelet effect. The antiplatelet effect of berberine has been discovered in some studies. Huang *et al.*, 2002 performed a series of experiments addressing its functions in preventing thrombus formation in arteries and assisting thrombolysis induced by the plasminogen activators. They successfully used berberine for patients with platelets of high aggregability (Huang *et al.*, 2002). Feng *et al.* reported its high efficiency in antiplatelet aggregation in patients with atherosclerotic cerebral infarction compared with aspirin (Feng *et al.*, 1996). It has been suggested that the mechanisms of the antiplatelet effects of berberine are due to its inhibitory effects on arachidonic acid metabolism (Wu and Liu, 1995) and calcium influx (Huang *et al.*, 1991a) and its effect on platelet $\alpha 2$-adrenoceptors as a partial agonist (Hui *et al.*, 1991; Huang *et al.*, 2002**)**.

In addition, pharmacological studies demonstrated other cardiovascular effects for berberine including preventing ventricular fibrillation that is related to its inhibitory effects on potassium channels (Zhang *et al.*, 1992; Li *et al.*, 2001), increase of I(Ca) (Wang and Zheng, 1997) and suppression of delayed afterdepolarizations, which may be attributable in part to a decrease in Na^+ influx (Wang *et al.*, 1994); cholesterol lowering activity via upregulation of low-density lipoprotein (LDL) receptor expression (Kong *et al.*, 2004; Abidi *et al.*, 2005; Cicero Arrigo *et al.*, 2007; Weijia *et al.*, 2004) inhibition of vascular smooth muscle cell (VSMC) (Lee *et al.*, 2006; Tanabe *et al.*, 2005) and human aortic intimal cell (Ren *et al.*, 1989) proliferation; preventing the ventricular hypertrophy induced by L-thyroxine in rats (Yang *et al.*, 2004); and alleviating ischemic/reperfusion injury in cardiac myocytes (Zheng *et al.*, 2003).

IMMUNE SYSTEM EFFECTS

Immunomodulation. The results of one study indicate that berberine has an immunosuppressive effect in the tubulointerstitial nephritis model, which is an analogue of various human kidney autoimmune diseases. In this study, flow cytometric analysis of peripheral blood cells showed that berberine caused a decrease in the number of CD3q, CD4q, CD8q and sIgq lymphocytes in comparison with TIN mice (Marinova *et al.*, 2000). In another study, berberine was used in the immunomodulation of adjuvant-induced arthritis in mice (Ivanovska and Philipov, 1996). The anticomplementary activity has been proposed as one of the possible mechanisms of this effect (Kostalova *et al.*, 2001). Berberine also inhibits *in vitro* cellular proliferation of human peripheral blood lymphocytes stimulated with phytohaemagglutinin, concanavalin A and pokeweed mitogen (Ckless *et al.*, 1995). Another study has suggested that berberine increases non-specific and decreases specific immunity in mice (Geng *et al.*, 1996).

Antiinflammatory. Extracts obtained from the roots and barks of various *Berberis* species are used as folk remedies worldwide for the treatment of various inflammatory ailments including lumbago and rheumatism and to reduce fever (Yeşilada and Küpeli, 2002). Many studies have been shown antiinflammatory and antinociceptive activity for *B. vulgaris* and berberine; but the exact mechanism is unknown (Yeşilada and Küpeli, 2002; Küpeli *et al.*, 2002; Ivanovska and Philipov, 1996). Berberine dose-dependently induced gastric ulcerations during acute toxicity testing (Awouters *et al.*, 1978; Küpeli *et al.*, 2002). Since it is well known that antiinflammatory agents that exhibit their activity through the inhibition of prostaglandin biosynthesis may induce gastric ulceration, the mechanism of antiinflammatory effect of berberine may also be based on this mechanism. It is noteworthy that powdered roots of *Berberis lycium* are advised to be taken with milk for the treatment of rheumatism and muscular pains in Pakistan folk medicine, probably to protect the stomach from this toxicity. Contrary to this conclusion, however, the extract of this species is also claimed to treat gastric and duodenal ulcers in a study from Pakistan (Yeşilada and Küpeli, 2002). Chi-Li Kuo has shown that in the oral cancer cell line OC2 and KB cells, a 12 h berberine treatment (1, 10 and 100 mM) reduced prostaglandin E2 (PGE2) production dose-dependently with or without 12-O-tetradecanoylphorbol-13-acetate (TPA, 10 nM) induction. This berberine induced effect occurred rapidly (3 h) as a result of reduced COX-2 protein, but not enzyme activity. Further analysis showed that berberine inhibits activator protein 1 (AP-1) a key transcription factor in inflammation and carcinogenesis (Kuo *et al.*, 2004). The antiinflammatory action of berberine, also may arise in part from the inhibition of DNA-synthesis in activated lymphocytes (Ckless *et al.*, 1995).

CENTRAL NERVOUS SYSTEM EFFECTS

Peng *et al.* showed using two experimental anxiety models in the mice (black and white test and elevated plus-maze test) that berberine (100, 500 mg/kg) has an anxiolytic effect which was similar to that observed with 1 mg/kg diazepam and 2 mg/kg buspirone. They concluded that the anxiolytic effect of berberine might be related to an increase in turnover rates of monoamines in the brain stem and decreased serotonergic system activity. Moreover, berberine decreased serotonergic system activity via activation of somatodendritic 5-HT1A autoreceptors and inhibition of postsynaptic 5-HT1A and 5-HT2 receptors (Peng *et al.*, 2004).

In Iranian traditional medicine, *B. vulgaris* fruit (barberry) is known for its sedative effect (Fatehi-Hassanabad *et al.*, 2005). Regarding the mechanism of this effect, one study showed that application of the *B. vulgaris* fruit extract (1–50 mg/mL) shifted the

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activation threshold voltage to more negative potentials, leading to an enhancement in magnitude of the outward potassium current recorded from cells present in rat brain slices of the parabrachial nucleus and cerebellum. This effect on potassium current may explain the sedative and neuroprotective effects of barberry (Fatehi-Hassanabad *et al.*, 2005). Also Fang Wang showed that berberine blocked transient outward potassium current and delayed rectifier potassium current in a concentration-dependent manner in acutely isolated CA1 pyramidal neurons of rat hippocampus using the whole-cell patch-clamp techniques. These results suggested that a block of potassium currents by berberine contributes to its protective action against ischemic brain damage (Wang *et al.*, 2004a). Berberine exerted NO-, O(2)(-)- and ONOO(-)-scavenging activities that may have a role in reducing oxidative damage (Yokozawa *et al.*, 2004). Other mechanisms that have been suggested in the neuroprotective effect of berberine include the inhibitory effects on norepinephrine, H_2O_2-induced [Ca^{2+}i] elevation (Wu *et al.*, 1997a), neurotransmitters-induced [Ca^{2+}i] elevation (Wu *et al.*, 1997b) and increasing the content of GSH (Wu *et al.*, 1999b).

Berberine after 7 days or 14 days administration significantly improved scopolamine-induced amnesia. This effect was significantly augmented by physostigmine or neostigmine, and completely reversed by scopolamine *N*-methylbromide suggesting an increase in the peripheral and central cholinergic neuronal system activity (Peng *et al.*, 1997).

Berberine acts as a reversible competitive inhibitor of acetylcholinesterase in a dose-dependent manner (IC_{50} = 3.3 μM) (Kim *et al.*, 2004; Whiteley and Daya, 1995), inhibits tyrosine hydroxylase leading to decreased dopamine content in PC12 cells (IC_{50} = 18.6 μM) (Shin *et al.*, 2000), inhibits tryptophan hydroxylase, a rate-limiting enzyme in serotonin biosynthesis (Lee *et al.*, 2001), inhibits lens aldose reductase (IC_{50} = 13.98 nM) (Lee, 2002) and competitively inhibits MAO-A (IC_{50} = 126 μM) (Kong *et al.*, 2001) and MAO-B (IC_{50} = 90 μM) (Castillo *et al.*, 2005).

Recently, it was shown that the extracts of barberry and berberine have some potential role in potentiating inhibitory neural pathway and decreasing morphine dependence, locomotor activity and inducing hypnosis (Nassiri-Asl *et al.*, 2007).

ENDOCRINE EFFECTS

In China in the 1980s, a hypoglycemic effect was accidentally found when berberine was administered to diabetic patients with diarrhea (Yin *et al.*, 2002). Since then berberine has often been used as an antihyperglycemic agent by many physicians in China. There have been substantial amounts of clinical and experimental reports about new actions of berberine (Pan *et al.*, 2003; Yin *et al.*, 2002). It was reported that berberine has a similar effect to metformin on improving insulin sensitivity in high-fat-fed rats (Yin *et al.*, 2002) and can act as an effective insulin sensitizing and insulinotropic agent in cell culture studies (Ko *et al.*, 2005). The results of other studies that used HepG2 and TC3 cell lines suggest that berberine is able to exert a glucose-lowering effect in hepatocytes, which is insulin independent and similar to that of metformin, but has no effect on insulin secretion (Yin *et al.*, 2002). Meanwhile, berberine effectively inhibits sucrase and maltase activity to the same extent as acarbose. However, gluconeogenesis and glucose consumption by Caco-2 cells was not influenced greatly. These results suggest that the antihyperglycemic activity of berberine is at least partly due to its ability to inhibit α-glucosidase. Furthermore, it may also decrease glucose transport through the intestinal epithelium to some extent (Pan *et al.*, 2003). The fact that berberine has low bioavailability and shows poor absorption through the gut wall (<5%) (Pan *et al.*, 2002) support the thesis that berberine may exert its antihyperglycemic effect in the intestinal tract before absorption.

Berberine inhibits the formation of osteoclast-like multinucleated cells in the co-culture of mouse osteoblastic cells and bone marrow cells in the presence of 1alpha,25-dihydroxyvitamin D3, PTH and interleukin-1alpha. The oral administration of berberine (30 and 50 mg/kg/day) to ovariectomized rats prevented a decrease in bone mineral density (BMD) of the lumbar vertebra without affecting the weight of the uterus and plasma concentration of estradiol. These results suggested that berberine prevented a decrease in BMD *in vivo* by inhibiting osteoclastic bone resorption (Li *et al.*, 1999). Also the oral administration of berberine (10 mg/kg/day) to male and female mice (senescence accelerated mice P6) for 22 weeks resulted in an increase in BMD in both sexes. But there was no effect on body or tibia weight or on the concentration of procollagen type I carboxyterminal extension peptide (PICP) in serum (Li *et al.*, 2003).

RESPIRATORY EFFECTS

Berberine can increase mucin release by directly acting on airway mucin-secreting cells suggesting this agent for further study for the possible use as a mild expectorant during the treatment of chronic airway diseases (Lee *et al.*, 2003).

GASTROINTESTINAL EFFECTS

Berberine has been widely used to treat gastroenteritis and diarrhea patients in the Chinese population for a long time (Lin *et al.*, 2005). Rabbani showed in a clinical trial that in adult patients with acute diarrhea due to enterotoxigenic *Escherichia coli* (ETEC) or *Vibrio cholerae*, berberine is an effective and safe drug, but it appears that berberine is more effective in *E. coli* diarrhoea than in cholera (Rabbani *et al.*, 1987; Rabbani, 1996). Another study showed that berberine reduced the cholera toxin-induced secretion of water, Na^+, Cl^+, and calculated residual ion (primarily HCO_3^-) in a concentration-dependent manner (Swabb *et al.*, 1981; Sack and Froehlich, 1982) and also has a direct bactericidal activity against *Vibrio cholera* (Amin *et al.*, 1969). Several mechanisms are involved in the antidiarrheal effect of berberine. As mentioned later, berberine acts as an antimicrobial agent. It also has a high binding affinity for mast cells (Berlin and Enerback, 1983) and

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influences mast cell-mediated chloride secretion in rat colon (Taylor and Baird, 1993). Berberine delays the small intestinal transit time (Yuan *et al.*, 1994). Berberine also possesses an inhibitory effect on the influx of extracellular Ca^{2+} and Ca^{2+}-release from intracellular stores in the smooth muscle cells of the colon; that may affect the tonicity of the colon (Cao *et al.*, 2001). Berberine exerts an anti-secretory action directly upon epithelial cells, probably by blocking K^+ channels (Taylor *et al.*, 1999). In the case of *Escherichia coli*, *in vitro* research indicated that berberine sulfate was capable of inhibiting bacterial adherence to mucosal or epithelial surfaces, the first step in the infective process. This may be a result of berberine's inhibitory effect on fimbrial structure formation on the surface of the treated bacteria (Sun *et al.*, 1988b). Other studies have shown the anticholinergic activity in isolated guinea-pig ileum of the aqueous extract of barberry fruits (Shamsa *et al.*, 1999) and also of berberine (Tsai and Ochillo, 1991).

Berberine has demonstrated growth inhibition *of Giardia lamblia* and *Entamoeba histolytica* (Kaneda *et al.*, 1991). Clinical trials conducted in India showed that berberine administration improved gastrointestinal symptoms and resulted in a marked reduction in *Giardia*-positive stools at half the dose of metronidazole. Berberine has rapid amoebicidal effects on *Entamoeba histolytica* and causes encystation, degeneration and eventual lysis of the trophozoite forms (Anonymous, 2000). Berberine also can inhibit the increased production of interleukin-8 in trinitrobenzene sulfonic acid-induced colitis, as a model of experimental colitis in rats (Zhou and Mineshita, 2000). As noted before, berberine inhibits COX-2 promoter activity that may be useful in the prevention and/or treatment of colorectal cancer (Fukuda *et al.*, 1999).

The pretreatment of animals with a single oral dose of berberine (4 mg/kg) induced prolongation of the pentobarbital (60 mg/kg, i.p.)-induced sleeping time suggestive of an inhibitory effect on microsomal drug metabolizing enzymes, cytochrome P450s (Janbaz and Gilani, 2000).

Berberine abolished acetaldehyde-induced NF-kappaB activity and cytokine production in a dose-dependent manner and therefore it was suggested to have a potential role in the treatment of alcoholic liver disease. It has been suggested that acetaldehyde-induced proinflammatory cytokine production in hepatic cells is related to alcoholic liver disease (Hsiang *et al.*, 2005). Berberine also has inhibitory effects on potassium and calcium currents in isolated rat hepatocytes (Wang *et al.*, 2004b), and reduces oxidative stress in living systems (Hwang *et al.*, 2002) which may be involved in hepatoprotection. Berberine has shown a choleretic action that on the basis of bilirubin output is similar to that of a known hydrocholeretic, α-hydroxy-1-cyclohexyl butyric acid (Hobara and Watanabe, 1984).

SKIN EFFECTS

A study showed that lipogenesis in the hamster sebaceous glands was suppressed 63% by 10^{-4} M berberine experimentally used for acne vulgaris (Seki and Morohashi, 1993).

Berberine increases effectively the skin permeation of polar drugs such as 5-fluorouracil similarly to surfactants (Namba *et al.*, 1995).

ANTIMICROBIAL EFFECTS

One of the most prominent clinical uses of *B. vulgaris* is in bacterial infection such as bacteria related diarrhea, parasitic intestinal infections and ocular infections (conjunctivitis, trachoma) (Birdsall and Kelly, 1997; Khosla *et al.*, 1992).

Berberine displayed a significant antibacterial and antifungal activity against *Staphylococcus aureus* and different *Candida* spp., (MIC = 64 μg/mL for *Candida albicans*) (Freile *et al.*, 2003). Other *in vitro* studies have shown that berberine is effective against *Entamoeba histolytica*, *Giardia lamblia*, *Trichomonas vaginalis* (Kaneda *et al.*, 1991), *Helicobacter pylori* (MIC_{50} = 12.5 μg/mL) (Mahady *et al.*, 2003) and *Leishmania donovani* (Ghosh *et al.*, 1985). The combination of amphotricine B and berberine can reduce by approximately 75% the amphotricine B dose in the treatment of candidiasis in mice, implying that berberine indeed has synergy with amphotricine B against *C. albicans* (Han and Lee, 2005). In chloroquine resistant malaria, the combination of pyrimethamine and berberine gives the best results in clearing the parasite and is more effective than both tetracycline and cotrimoxazole (Sheng *et al.*, 1997). Berberine also inhibits *T. vaginalis* and its effect is comparable to metronidazole as regards potency (Soffar *et al.*, 2001). In the mechanistic aspect, one study has shown that berberine has potent inhibitory activity against sortase A (SrtA) and sortase B. The inhibition of sortase enzymes results in a marked reduction in the virulence and infection potential of *S. aureus*, so it may be an important mechanism in the antibacterial activity of berberine (Oh *et al.*, 2006). Berberine interferes with the adherence of group A streptococci to host cells by preventing the complexing of lipoteichoic acid with fibronectin or by dissolution of such complexes once they were formed (Sun *et al.*, 1988b) and also inhibits the adhesion of uropathogenic *E. coli* to epithelial cells by a reduction in the synthesis of fimbrial subunits (Sun *et al.*, 1988a).

A clinical study of aqueous berberine versus sulfacetamide for the treatment of *Chlamydia trachomatis* infection showed that while sulfacetamide eye drops produced slightly better clinical results, conjunctival scrapings of these patients remained positive for the infective agent and relapses occurred. In contrast, the conjunctival scrapings of patients receiving the berberine chloride eye drops were negative for *C. trachomatis* and there were no relapses, even 1 year after treatment. It was also concluded that, while berberine chloride had no direct antichlamydial properties, it seemed to cure the infection by stimulating some protective mechanism in the host. A second clinical study found berberine chloride superior to sulfacetamide in both the clinical course of trachoma and in achieving a drop in serum antibody titers against *C. trachomatis* (Anonymous, 2000).

Moreover, several studies have shown that plants of the genus *Berberis* (*B. repens*, *B. aquifolium* and *B. fremontii*) producing berberine, also synthesize two

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substances, the flavonolignan 5′-methoxyhydnocarpin and the porphyrin pheophorbide A (Fig. 1), which have no antibacterial activity but have an inhibitory property against the multi-drug resistant (MDR) efflux pumps found so far in *S. aureus* (Stermitz *et al.*, 2001, 2000).

The MDR pumps extrude synthetic and natural antimicrobials from bacterial cells. For example, Musumeci confirmed the presence of pheophorbide in *B. aetnensis* that improved the activity of ciprofloxacin by inhibition of MDR pump (Musumeci *et al.*, 2003).

TOXICOLOGY

Berberis vulgaris is moderately toxic ($LD_{50} = 2.6 \pm 0.22$ g/kg b.w. in mice) (Peychev, 2005). Berberine is not considered toxic at the doses used in clinical situations, nor has it been shown to be cytotoxic or mutagenic. Side-effects can result from high dosages and may include gastrointestinal discomfort, dyspnea, lowered blood pressure, flu-like symptoms and cardiac damage. Berberine usage should be avoided in pregnancy, due to a potential for causing uterine contractions and miscarriage, and in jaundiced neonates because of its bilirubin displacement properties. The therapeutic dosage for most clinical situations is 200 mg orally two to four times daily (Anonymous, 2000). Berberine displays a dose-dependent inhibition of arylamine *N*-acetyltransferases (NAT) activity and gene expression (NAT mRNA) and the levels of NAT protein in mouse and human leukemia cells, human bladder tumour cells and a human colon tumor (adenocarcinoma) cells. Regarding the role of NATs in the metabolism of arylamine chemicals and carcinogens in generating intermediate metabolites and finally cancer in specific target organs or tissues, and polymorphic NAT is thought to involve a cancer risk related to environmental exposure, berberine may be considered as a protective agent against carcinogens (Chung *et al.*, 1999; Lin *et al.*, 1999b; Chung *et al.*, 2000; Lin *et al.*, 2005). In a study, berberine completely blocked cyclophosphamide-induced bladder edema and hemorrhage in rats. Therefore, it seems that berberine could be a potential drug in the treatment of cyclophosphamide-induced cystitis (Xu and Malave, 2001). Co-administration of berberine with cyclosporine A can reduces the renal toxicity of cyclosporine A in recipients undergoing cardiac transplantation (Ni *et al.*, 2003). Berberine showed a significant concentration-dependent inhibitory effect against the acridine orange-induced chloroplast mutagenesis of *Euglena gracilis* as a eukaryotic test model (Cernakova *et al.*, 2002).

Berberine activates the aryl hydrocarbon receptor (AhR) in human hepatoma (HepG2) and rat hepatoma cells, but it is accompanied by inactivation of the catalytic activity of CYP1A1 and occurs at concentrations that exceed those predicted to occur *in vivo*. Therefore, it appears that activation of the AhR pathway by berberine has a low toxicological potential (Vrzal *et al.*, 2005). Berberine is able to produce radical species in a nonpolar environment. UVA irradiation of HaCaT keratinocytes in the presence of 50 μM berberine resulted in an 80% decrease in cell viability and a 3-fold increase in DNA damage as measured by the comet assay. Therefore, exposure to sunlight or artificial light sources emitting UVA should be avoided when topical preparations containing berberine are used (Inbaraj *et al.*, 2001).

CYTOTOXIC EFFECTS

Berberine has shown a strong inhibition on the proliferation of both hepatoma and leukemia cell lines, with IC_{50} values varying from 1.4 to 15.2 μg/mL (Lin *et al.*, 2004a). For example, berberine showed cytotoxicity against HeLa (uterus carcinoma), SVKO3 (ovary carcinoma), Hep-2 (larynx carcinoma), primary culture from mouse embryo, human fibroblast cells (LC_{50} = 10 ppm for all cell lines) (Orfila *et al.*, 2000), human and rat malignant brain tumors (Zhang *et al.*, 1990) and two types of esophageal cancer cell lines (YES-3 and YES-4) (Iizuka *et al.*, 2000b).

Berberine had been demonstrated to inhibit DNA, RNA and protein synthesis in sarcoma S180 cells *in vitro* (Creasey, 1979). Berberine-treated HL-60 cells had an increased G2/M phase population (Kuo *et al.*, 1995) associated with down-regulation of nucleophosmin/B23 and telomerase activity (Wu *et al.*, 1999a).

On the other hand, it is also reported that berberine modulates the expression of the MDR1 gene product and the responses of digestive tract cancer cells to paclitaxel (Lin *et al.*, 1999a).

The ability of these compounds to act as topoisomerase poisons (topoisomerase I and II), has been suggested as another mechanism of antitumor activity (Li *et al.*, 2000; Kettmann *et al.*, 2004; Mazzini *et al.*, 2003). Wu *et al.* suggested that the cytotoxic effect of berberine in cancer cells may be due partially to its direct blockade of voltage- and Ca-dependent K^+ channels (Wu *et al.*, 1998). In another study, the apoptotic effect of berberine on KB cells has been attributed to COX-2 inhibition via decrease of Akt phosphorylation and Mcl-1 expression (Kuo *et al.*, 2005). Berberine showed an inhibition of reverse transcriptase activity of RNA tumor viruses that may contribute to the antileukemic activity of this alkaloid (Sethi, 1983). Another study showed that treatment with a nontoxic dose of berberine rendered glioblastoma multiforme cells more sensitive than vehicle-treated control cells to x-rays and suggests that berberine could be integrated with postoperative radiotherapy to selectively promote residual glioblastoma multiforme tumor cell death (Yount *et al.*, 2004).

Berberine showed potent antiangiogenic activity that can be used in cancer therapy (Lin *et al.*, 2004b). This effect is via the down-regulation of matrix metalloproteinases expression (Wartenberg *et al.*, 2003). In a study, berberine dose-dependently inhibited the secretion of IL-6 in a human esophageal cancer cell line *in vitro* and reduced IL-6 mRNA expression. These results suggest that berberine may have an anticachectic effect on esophageal cancer since numerous studies have suggested that circulating IL-6 secreted from tumor cells plays an important role in cancer-induced cachexia (Iizuka *et al.*, 2000a).

PHARMACOKINETIC INTERACTION

Berberine can markedly elevate the blood concentration of cyclosporine A (CsA) in renal-transplant

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recipients and healthy volunteers necessitating a reduction of the cyclosporine dosage. This effect of berberine may be partly attributed to a decrease in liver and/or intestinal metabolism through the inhibition of CYP3A4 in the liver and/or gut wall. The berberine-induced increase in emptying time of the stomach and small intestine might be another reason for the increase in CsA bioavailability (Wu *et al.*, 2005; Xin *et al.*, 2002, 2006).

As noted before, berberine has poor intestinal absorption. P-glycoprotein appears to contribute to the poor intestinal absorption of berberine which suggests that P-glycoprotein inhibitors such as cyclosporine A and verapamil could be of therapeutic value by improving its bioavailability (Pan *et al.*, 2002).

Berberine causes displacement of bilirubin from albumin, about tenfold more than phenylbutazone, a known potent displacer of bilirubin. Therefore, the use of the herb containing a high proportion of berberine is best avoided in jaundiced neonates and pregnant women (Chan, 1993). Berberine also displaces warfarin, thiopental and tolbutamide from their protein binding site, increasing the blood level of the free drug, and enhancing their actions or toxicity (Tan *et al.*, 2002).

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