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Review

Bioactivities of Berberine: An Update

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Abstract: Berberine has been used in traditional medicines. Recently, it has intrigued increasing interest on its various significant bioactivities. In this review, the latest studies on berberine were updated, including its natural sources, extraction and detection methods, absorption and metabolism, and bioactivities. Furthermore, especial attention was paid to its bioactivities, such as antioxidant, anti-microbial, anti-cancer, cardiovascular protective, anti-diabetic, neuroprotective, anti-obesity, hepatoprotective, gastrointestinal protective, anti-rheumatic, anti-angiogenic and anti-clastogenic effects, and potential mechanisms. The accumulated evidence could provide theoretical basis for its future application in clinic to prevent and treat diseases.

Keywords: berberine; separation; absorption; metabolism; bioactivities; mechanisms.

1. Introduction

Berberine (Fig. 1), a natural isoquinoline alkaloid with an intense yellow color and a bitter taste, is found in many medicinal plants used in traditional Indian and Chinese medicine. Since it is strongly yellow-colored, it is also used as a dye named “natural yellow 18”, being one of the yellow dyes deriving from natural sources. In recent decades, berberine has intrigued increasing interest in its significant bioactivities, such as antioxidant, anti-microbial and anti-cancer effects. This review mainly provided latest information about the researches on berberine. Firstly, its natural sources were introduced. Then, the extraction and detection methods were summarized. Next, its absorption and metabolism were stated. Finally, its bioactivities were specially highlighted.

2. Natural Sources of Berberine

A number of medicinal plants, such as *Coptidis rhizome* and Barberry plants, are the major natural sources of berberine. Researches found that berberine is mainly distributed in the roots, barks and stems of plants. *Coptidis rhizome* (also named *Coptis chinensis* and Huanglian) is a famous herb

used in traditional Chinese medicine for centuries to clear heat, dry dampness, purge fire and eliminate toxin, and its yellow roots contain a high content of berberine (Tang et al., 2009; Wu et al., 2010). Barberry plants, including *Berberis aristata, Berberis aquifolium, Berberis asiatica, Berberis croatica, Berberis thunbergii* and *Berberis vulgaris,* are shrubs mainly grown in Asia and Europe, especially in India and Iran, and their roots, barks, leaves and fruits are often used as folk medicine (Andola et al., 2010; Imanshahidi and Hosseinzadeh, 2008; Kosalec et al., 2009; Kulkarni and Dhir, 2010). Other berberine-containing medicinal plants include *Tinospora cordifolia* fruits (Khan et al., 2011), *Hydrastis canadensis* (Imanshahidi and Hosseinzadeh, 2008), and *Coscinium fenestratum* (Rojsanga et al., 2006).

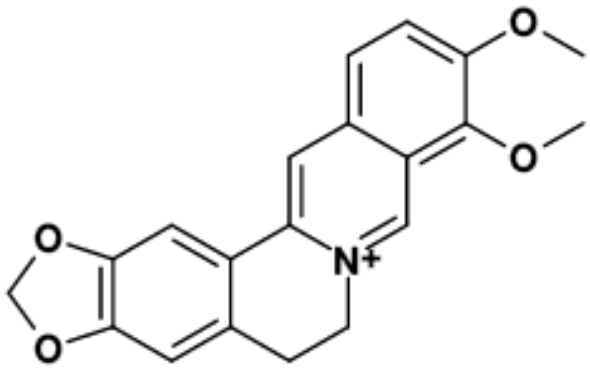

Figure 1. The chemical structure of berberine

3. Extraction and Detection of Berberine

3.1. Extraction Methods

Highly purified berberine is prerequisite to research its bioactivities. Therefore, the extraction methods are important to get a purified berberine. Firstly, medicinal plants should be dried and powdered in order to increase the extraction efficiency. Then, it was defatted with petroleum ether (60-80 □), and the marc was dried and further extracted by methanol (Srinivasan et al., 2008), or it could be directly extracted by water (Narasimhan and Nair, 2005) or some organic solvents, such as acetonitrile solution (Brown and Roman, 2008) as well as methanol and 95% ethanol with 1,2-propanediol-modified supercritical carbon dioxide (Liu et al., 2006). Finally, raw extracts could be further separated and purified by many methods, such as high performance liquid chromatography (HPLC).

3.2. Detection Methods

A variety of detection methods, such as chromatographic and spectroscopic methods, were used to detect and analyze berberine.

Chromatography was the most commonly used method to determine berberine in various samples. HPLC was reported to analyze berberine in medicinal plants (Kamal et al., 2011), tissues

(Wang et al., 2005) and plasma (Liu et al., 2011; Srinivasan et al., 2008). A liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) method could also determine berberine in the plasma (Hua et al., 2007; Liu et al., 2011). Another chromatography method, high-performance thin-layer chromatography (HPTLC), was also reported to quantify berberine content in herbal extract and pharmaceutical dosage form, with a rapid, accurate, and cost-effective characteristics (Ghosh et al., 2010; Rout et al., 2008).

In addition, spectroscopic-based methods were often employed to detect berberine. A light-emitting diode induced fluorescence microplate analyzer could detect berberine in pharmaceutical preparation and medicinal herbs with high recoveries (> 95%) (Zhang et al., 2011). Another spectrofluorimetric method, based on significant fluorescence enhancement by supramolecular complex formation between berberine and chloride, was also used to determine berberine in tablets, serum and urine samples with high sensitivity and selectivity (Dong et al., 2011). Using water-soluble CdTe quantum dots as probes, a fluorescence quenching method could also be employed for berberine determination (Cao et al., 2010). Selective and affinitive imprinted polymers, such as polymer AD-10, cooperating with spectrophotometric analysis, was used to determine berberine from natural products, and this method had good efficiency, specificity and selectivity (Chen et al., 2011). ^{1}H-NMR spectroscopy was reported to directly detect berberine contents in *Coptidis rhizoma* and the purities of commercial reagents of protoberberine alkaloids (Hasada et al., 2011; Li et al., 2009). The near-infrared (NIR) diffuse reflectance spectroscopy combined with the artificial neural network (ANN) was also a rapid and accurate method to detect the content of Berberine in the processed Coptis (Zhang et al., 2008). Resonance Rayleigh scattering spectrum (RRS) spectrum method was a highly sensitive, simple and rapid method to detect trace amounts of berberine in pharmaceuticals and goldthread extracts (Peng et al., 2005). Other methods, such as capillary electrophoresis coupled with end-column electrochemiluminescence (ECL) detection, were applied to determine berberine in tablets and medicinal plants, such as *Rhizoma coptidis* (Du and Wang, 2010).

4. Absorption and Metabolism of Berberine

4.1. Absorption of Berberine

Berberine is mainly absorbed in the intestinal tract. However, it has a poor absorption and a low bioavailability. After administrated via the femoral vein and oral gavage, little berberine was absorpted from rat gastrointestinal tract, and the absolute bioavailability of berberine in rats was reported to be only 0.68% (Chen et al., 2011), which is comparable with the result of another research that the absolute oral bioavailability of berberine in rats was merely 0.36% (Liu et al., 2010). The mechanisms of the low absorption and bioavailability of berberine remain incompletely understood, however, recent studies have proposed some interpretation. Firstly, the structure of berberine limited its absorption. Berberine, as a hydrophilic compound determinted by its structure, was lipophobic and hard to pass through the plasma membrane of intestinal cells (Chen et al., 2011). Secondly, the intestinal first-pass elimination of berberine was extensive. After intragastric administration, only half of berberine could be kept intact through the gastrointestinal tract, meanwhile another half was disposed by the small intestine (Liu et al., 2010). Finally, ATP-binding cassette (ABC) transporters

might directly efflux the absorbed berberine back into the intestinal lumen. It was reported that berberine was the substrate of several ABC transporters, such as P-glycoprotein (P-gp, also named multidrug resistance protein1 (MDR1)) and multidrug resistance-associated protein (MRP) (Maeng et al., 2002; Shitan et al., 2007). In a cell model, the uptake of berberine depended on the cellular ATP level and its accumulation was less in the cells expressing MDR1 or MRP1 (Shitan et al., 2007). And the inhibitors of MDR1, but not MRP1 or MRP2, could increase the uptake of berberine in Coca-2 cells (Kulkarni and Dhir, 2010; Zhang et al., 2011). By and large, the low absorption and bioavailability of berberine was with complex mechanisms.

Since berberine has many important bioactivities, to increase its absorption and bioavailability may significantly enhance its beneficial effects. Recent years, several methods have already been found to increase its absorption and bioavailability. Several compounds, such as chitosan, lysergol, D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) and sodium caprate, were reported to increase the absorption and bioavailability of berberine in animal models. Chitosan could increase berberine absorption in a dose-dependent manner, probably by improving the paracellular pathway of berberine in rat intestinal tract (Chen et al., 2012). Lysergol, an alkaloid of the ergoline family, could enhance the oral bioavailability of berberine in rats through increasing its stability in rat plasma (Patil et al., 2011). TPGS could enhance berberine absorption in rats, probably through inhibiting the action of P-gp and decreasing the efflux of absorbed berberine into the intestinal lumen (Chen et al., 2011). Sodium caprate could stimulate mucosal-to-serosal transport of berberine, therefore significantly increase the absorption of berberine in the intestine and its concentration in the plasma, as well as enhance its anti-diabetic effect (Lv et al., 2010). Nanoparticle carriers could also increase berberine oral bioavailability. By preparing berberine nanoparticles, anhydrous reverse micelle (ARM) delivery system could improve its oral bioavailability and anti-diabetic efficacy (Wang et al., 2011). Another nanoparticle berberine carrier with a heparin shell could effectively control the release of berberine and treat Helicobacter pylori infection (Chang et al., 2011). Likewise, some formulations could improve the bioavailability of berberine. In rats, an oral microemulsion formulation of berberine with pharmaceutically acceptable ingredients, such as oleic acid, Tween 80 and PEG400, could improve the bioavailability of berberine compared to the berberine tablet suspensions (Gui et al., 2008). In healthy male volunteers, *Rhizoma coptidis* granules combined with cinnamon granules could promote berberine absorption, increase its plasma concentration and detention time (Huang et al., 2011).

Berberine has a wide range of distribution in vivo. Compared to other organs, I^{125}-labeled berberine was highly found in the gallbladder and gastrointestinal system (Li et al., 2005). It was also able to cross the blood-brain barrier (BBB) and enter the brain, such as the thalamus (Wang et al., 2005) and hippocampus (Wang et al., 2005), which indicated that berberine might have protective effects on central nervous system.

4.2. Metabolism of Berberine

The intestine and liver are both involved in the metabolism of berberine in vivo. In the intestine, intestinal bacteria was reported to be responsible for metabolizing berberine, and played an important role in the enterohepatic circulation of its metabolites (Zuo et al., 2006). There were three major berberine metabolites found in the rat intestine (Liu et al., 2010). Liver is known to metabolize

different kinds of compounds, and it is also the major organ for berberine metabolism. Oxidative demethylenation and the subsequent glucuronidation in liver were the major metabolic pathways of berberine in rats (Liu et al., 2009). After metabolized in the liver, the metabolites of berberine were mainly excreted in the urine through kidney, and small parts could be excreted through the hepatobiliary tract into the intestinal tract (Li et al., 2005). Cytochromes P450 (CYPs), the major phase-I enzymes, was thought to take part in the oxidative demethylenation of berberine in the liver, and UGT1A1 and UGT2B1 were responsible for their subsequent glucuronidation (Liu et al., 2009). The major metabolites of berberine in the plasma and liver were oxidative metabolites M1 (via demethylation) and M2 (via demethylenation) and their corresponding glucuronides (Li et al., 2011; Liu et al., 2009). However, berberine had much more metabolites in the feces and urines. A study showed that eleven berberine metabolites were identified in the feces and urine of mice, including five unconjugated metabolites mainly in the feces, and six glucuronide and sulfate conjugates predominantly in the urine (Guo et al., 2011). Another study indicated that after oral administration of berberine, seven metabolites (HM1-HM7) were found in the human urine, including demethyleneberberine-2-O-sulfate (HM1), jatrorrhizine-3-O-β-D-glucuronide (HM2), thalifendine-10-O-β-D-glucuronide (HM3), berberrubine-9-O-β-D-glucuronide (HM4), jatrorrhizine-3-O-sulfate (HM5), 3,10-demethylpalmatine-10-O-sulfate (HM6) and columbamin-2-O-β-D-glucuronide (HM7), as well as five metabolites (RM1-RM5) were identified from the rat urine, including demethyleneberberine-2,3-di-O-β-D-glucuronide (RM1), berberrubine-9-O-β-D-glucuronide (RM2), demethyleneberberine-2-O-sulfate (RM3), 3,10-demethylpalmatine-10-O-sulfate (RM4) and thalifendine (RM5) (Qiu et al., 2008). Therefore, it is complicated for the metabolism of berberine in vivo.

5. Bioactivities of Berberine

Berberine has been reported to have a range of bioactivities. These beneficial effects could be helpful for the prevention and treatment of many diseases, such as cancer, cardiovascular diseases, diabetes, neurodegenerative diseases, etc. The following part mainly summarized recent researches on its bioactivities, as well as the potential mechanisms.

5.1. Antioxidant Effect of Berberine

Oxidative stress has been implicated in the pathophysiologic process of many chronic inflammatory and degenerative diseases. The generation of reactive oxygen species (ROS) during oxidative stress can damage DNA, protein and cells, and play an important role in the disease progress. Natural antioxidants, such as polyphenols from medicinal plants, can quench ROS and strengthen the endogenous antioxidant defence system, therefore often used to prevent and treat oxidative stress-mediated diseases.

Berberine was reported to have high antioxidant ability (Shan et al., 2011). In vitro experiments, it had significant reductive ability and radicals scavenging capacity. In a concentration dependent manner, it could effectively scavenge 2, 2-azino bis (3-ethylbenzothiazoline-6-sulfonate) (ABTS), 2, 2-diphenyl 1-picrylhydrazyl (DPPH) and nitric oxide radicals, and inhibit lipid peroxidation (Shirwaikar et al., 2006). It could also protect cells from oxidative damage. In hydrogen

peroxide (H_2O_2)-induced PC12 cell, it could decrease lactate dehydrogenase (LDH) release, ROS content, and malondialdehyde (MDA) levels, thus inhibit cell apoptosis and increase cell viability (Xu and Zhou, 2010). Similarly, 10-1000 μmol/L berberine could inhibit the damaging effects of H_2O_2 in cultured rabbit corpus cavenosum smooth muscle cells (CCSMC) by increasing superoxide dismutase (SOD) activity and decreasing LDH release and MDA content (Tan et al., 2007). In THP-1 monocyte-derived macrophages, pre-treatment with berberine could inhibit NADPH oxidase-mediated superoxide anon generation in a concentration (10-50 mmol/L) and time (6-24 h) dependent manner, through selective inhibition of gp91 (phox) expression and enhancement of SOD activity (Sarna et al., 2010). In crucian carp, it was reported to inhibit the activities of oxidase cytochrome P4501A (CYP1A) and CYP3A, which could catalyze the oxidation of organic substances (Zhou et al., 2011). In diabetic rats, it could significantly decrease MDA level while increase catalase, SOD, glutathione peroxidase, and glutathione activities in liver tissue (Zhou and Zhou, 2011). Therefore, berberine may be a good candidate for natural antioxidant.

5.2. Anti-microbial Effects of Berberine

Berberine has been used as an anti-microbial reagent for a long history because of its effects on various microbes, such as virus, bacteria, fungi and protozoans. Table 1 lists recent studies on the anti-microbial effect of berberine and its derivates.

The mechanisms of berberine-mediated anti-microbial effects remain incompletely understood. However, several recent studies increased our knowledge in this area. Berberine could inhibit influenza virus growth and infection in cells, probably by inhibiting virus protein trafficking/maturation and inflammatory substances release-induced pathogenic changes (Cecil et al., 2011; Wu et al., 2011). Its anti-HPV effect might be through inhibiting AP-1 and blocking viral oncoproteins E6 and E7 expression in cervical cancer infected with HPV (Mahata et al., 2011). Its anti-HIV effect might be partly via suppressing RTase activity and inhibiting HIV protease inhibitor-induced inflammatory response (Bodiwala et al., 2011; Zha et al., 2010). It could also inhibit herpes simplex virus (HSV), probably through interfering with the viral replication cycle (Chin et al., 2010). Berberine-mediated anti-bacterial effect was probably through inhibiting bacterial division protein FtsZ (Boberek et al., 2010). In *Escherichia coli*, it could interact with FtsZ protein, and destabilize FtsZ protofilaments as well as inhibit the FtsZ GTPase activity (Domadia et al., 2008). Berberine could inhibit Aspergillus fumigates through the ergosterol biosynthesis pathway (Gao et al., 2011). In macrophages, berberine chloride-mediated anti-leishmanial activity was through activating p38 MAPK along with inhibiting ERK1/2 (Saha et al., 2011). Berberine chloride could also induce Leishmania donovani promastigote apoptosis-like death accompanying with increased generation of reactive oxygen species (Saha et al., 2009).

5.3. Anti-cancer Effect of Berberine

Recent years, berberine was reported to be a potential candidate for cancer treatment, because it could effectively fight against a variety of cancer cells. Its anti-cancer effect was mainly attributed to its actions on inducing cancer cell death, suppressing cancer cell growth and inhibiting cancer cell metastasis. The following part focused on its different actions on cancer cells.

5.3.1. Induction of cancer cell death

It was found that berberine could induce cell death in diverse cancer cells, such as breast cancer, liver cancer and lung cancer. Apoptosis was the most common way involved in berberine-induced cancer cell death in many cell lines and cancer cell xenograft (Choi et al., 2009). On the other hand, autophagy and necrosis were also reported to be associated with berberine-induced cancer cell death (Hou et al., 2011; Letasiova et al., 2006).

Table 1. Different Anti-Microbial Effects of Berberine

Anti-microbial effects	Microbe	References
Anti-viral effect	H1N1 influenza A virus	Cecil et al., 2011
	Human cytomegalovirus	Hayashi et al., 2007
	Human immunodeficiency virus (HIV)	Mahata et al., 2011; Zha et al., 2010
	Human papillomaviruse	Mahata et al., 2011
	Herpes simplex virus (HSV)	Chin et al., 2010
Anti-bacterial effect	*Aeromonas hydrophila*	Zhang et al., 2010
	Bifidobacterium adolescentis	Yan et al., 2009
	Edwardsiella ictaluri	Zhang et al., 2010
	Escherichia coli	Domadia et al., 2008; Zhang et al., 2010
	Pseudomonas fluorescens	Zhang et al., 2010
	Staphylococcus aureus	Kim and Son, 2005; Yu et al., 2005
	Staphylococcus epidermidis	Wang et al., 2009
	Streptococcus agalactiae	Zhang et al., 2010
	Vibrio vulnificus	Zhang et al., 2010
Anti-fungal effect	Aspergillus fumigates	Gao et al., 2011; Park et al., 2010
	Candida	Park et al., 2010; Wei et al., 2011
	Cryptococcus neoformans	Park et al., 2010
Anti-protozoal effect	Leishmania	Bahar et al., 2011; Saha et al., 2009 & 2011
	Plasmodium	Bahar et al., 2011
	Trypanosome	Bahar et al., 2011

Berberine could activate mitochondria and caspase-dependent apoptotic pathway in vitro (Patil et al., 2010). In cultured cancer cell lines, it could induce the disruption of the mitochondrial transmembrane potential, release of cytochrome c and apoptosis-inducing factor from the mitochondria to the cytosol (Burgeiro et al., 2011; Ho et al., 2009; Wang et al., 2010). It could also up-regulate the expression of pro-apoptotic Bax and Bak, activate ROS-mediated ER stress, and down-regulate the expression of anti-apoptotic Bcl-2 and Bcl-xl (Chen et al., 2009; Eom et al., 2010; Katiyar et al., 2009; Lin et al., 2006). Finally, a number of caspases, such as caspases 3, 4, 7, 8, and 9, could be activated by berberine (Burgeiro et al., 2011; Yan et al., 2011). On the other hand, the death receptor pathway was

activated in berberine-induced apoptosis (Lin et al., 2007). In human cervical carcinoma cells (HeLa), berberine could increase the expression of Fas, FasL, TNF-α and TRAF-1, which could initiate cell apoptosis, and subsequently activate caspase-3 and caspase-8 mediated cell apoptosis (Lu et al., 2010). Besides, berberine could regulate caspase-independent cell death by inducing DNA strand break through inhibition of topoisomerases and induction of DNA damage (Pinto-Garcia et al., 2010).

Many other apoptotic-related molecules were also reported to be involved in berberine-induced cell apoptosis. Berberine could up-regulate the expression of p53 and p27, which play a pro-apoptotic role in cancer cells (Lu et al., 2010; Patil et al., 2010). It could also induce the acetylation of α-tubulin and this correlated with the induction of apoptosis (Khan et al., 2010). In HER2-overexpressing breast cancer cells, it could promote cell apoptosis via down-regulating the HER2/PI3K/Akt signaling pathway (Kuo et al., 2011). Similarly, in SK-MEL-2 cell line, inhibition of B-RAF/ERK survival signaling pathway was involved in berberine-induced cell apoptosis (Burgeiro et al., 2011). In human ductal breast epithelial tumor cell line (T47D cell line) and human erythro-myeloblastoid leukemia cell line (K562 cell line), cyclooxygenase-2 (COX-2) and survivin, two anti-apoptotic proteins, could be inhibited by berberine (Pazhang et al., 2011 & 2012). In human hepatoma carcinoma cell lines (HepG2 and SMMC7721 cell lines), it could induce cell apoptosis by downregulating CD147 (Hou et al., 2011). In human renal cancer cell line (Caki cells), it could sensitize TRAIL-induced apoptosis through down-regulating c-FLIP and Mcl-1 proteins and inducing the expression of GADD153, a transcription factor involved in apoptosis (Lee et al., 2011; Lin et al., 2007). Berberine could also inhibit the oncogentic H-Ras and c-fos in T24 bladder cancer cell line (Yan et al., 2011).

Meanwhile, berberine could induce cancer cell death via autophagy and necrosis. In human hepatic carcinoma cell lines (HepG2 and MHCC97-L), berberine might induce autophagic cell death with the mechanism of inducing Beclin-1 activation and mTOR inhibition by suppressing the activity of Akt and up-regulating P38 MAPK signaling (Wang et al., 2010). In berberine-treated murine melanoma B16 cell line, necrosis could be observed based on the damage of cell membrane integrity (Letasiova et al., 2006).

5.3.2. Suppression of Cancer Cell Growth

It was reported that berberine could suppress the growth and proliferation of different cancer cells. Cell cycle arrest was the main mechanism involved in berberine-induced suppression of cancer cell growth in vitro. Berberine could induce cell cycle arrest at different cell cycle phases. It could promote cell cycle arrest at G0/G1 checkpoint in different cancer cell lines, such as MCF-7 and MDA-MB-231 breast cancer cell lines and human pulmonary giant cell carcinoma cell line (PG) (Kim et al., 2010; Luo et al., 2008). Berberine-mediated G0/G1 cell cycle arrest might be partly via inhibiting the expression of cyclin D1 (Luo et al., 2008). It could also induce G1-phase cell cycle arrest. For example, In HER2-overexpressing breast cancer cells, BIU-87 and T24 bladder cancer cell lines, lung tumor cells, osteosarcoma cells, human epidermoid carcinoma A431 cells, human glioblastoma T98G cells and prostate cancer cell lines (DU145, PC-3 and LNCaP cells), it could induce G1-phase cell cycle arrest (Eom et al., 2008; James et al., 2011; Kuo et al., 2011; Liu et al., 2009; Mantena et al., 2006; Yan et al., 2011). Berberine-induced G1-phase cell cycle arrest might be dependent on p53 (Liu et al., 2009), and regulated through increasing the expression of Cclk inhibitory proteins (Cdki), such

as Cip1/p21 and Kip1/p27**,** inhibiting the expression of cyclin-dependent kinase (Cdk) 2, Cdk4, Cdk6 and cyclins D1, D2 and E, as well as enhancing the binding of Cdki to Cdk (Mantena et al., 2006a & b). In addition, G1/S and G2/M phase cell cycle arrests were involved in berberine-induce cell cycle arrest. In HL-60 cells, berberine caused cell accumulation in S-phase via a strong activation of Chk2, phosphorylation and degradation of Cdc25A, and inhibition of Cdc2 (CDK1) and the proto-oncogene cyclin D1 (Khan et al., 2010). In NCI-H838 cell line, berberine could suppress cell growth via inducing G2/M arrest (Tungpradit et al., 2011). In human pancreatic cancer cells and human pronzyelocytic leukemia HL-60 cells, it could simultaneously inhibit G1/S and G2/M cell cycle phases by up-regulating the levels of Wee1 and down-regulating the levels of Cdc25c, CDK1 and cyclin B1 (Lin et al., 2006; Pinto-Garcia et al., 2010).

Except cell cycle arrest, berberine could suppress cell growth in other ways. In MCF-7 breast cancer cells, berberine could inhibit cell growth partly via reducing side population (SP) cells and ABCG2 expression (Kim et al., 2008). Besides, in Ehrlich ascites carcinoma cells, berberine could inhibit cell proliferation by induction of DNA damage, inhibition of DNA and protein synthesis (Letasiova et al., 2006).

Berbeirne also inhibited tumor growth in vivo. In both p53 expressing and p53 null lung tumor xenografts, orally administration of berberine could inhibit the growth of tumor cells in vivo (James et al., 2011; Katiyar et al., 2009). In a xenograft mouse model implanted with human tongue cancer SCC-4 cells, treatment of berberine could reduce the tumor incidence and tumor size (Ho et al., 2009).

5.3.3. Inhibition of Cancer Cell Metastasis

Several important factors, such as ECM proteinases, play an important role in cancer cell metastasis, and inhibition of these factors can suppress cancer cell migration and invasion. Recent studies found that berberine could exert its anti-cancer effect partly by inhibiting cancer cell migration, invasion and metastasis.

Berberine could inhibit two major ECM proteinases, matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator (u-PA), in cancer cell lines. In human hepatoma HepG2 cell line, it could inhibit cell invasion through suppression of MMP-9 expression through PI3K-AKT and ERK pathways (Liu et al., 2011). In human SCC-4 tongue squamous cancer cells, it could down-regulate u-PA, MMP-2 and -9 expression via the FAK, IKK and NF-κB -mediated signaling pathways (Ho et al., 2009). In MDA-MB-231 human breast cancer cells, it could suppress cell invasion by inhibiting TNF-α-induced MMP-9 expression through down-regulation of AP-1 activity (Kim et al., 2008). In human gastric cancer SNU-5 cells, it could prevent cell migration through inhibition of MMP-1, -2 and -9 gene expression (Lin et al., 2008). In human lung cancer cell line (A549 cells), it could inhibit cell invasion via reducing MMP2 and u-PA expression (Peng et al., 2006). Inhibition of Rho GTPases was also involved in berberine-mediated suppression of cancer cell migration. Berberine was reported to suppress cancer cell migration by inhibiting the activation of RhoA, Cdc42 and Rac1 Rho GTPases (Tsang et al., 2009). In a nasopharyngeal carcinoma cell line (5-8F), berberine could suppress Rho GTPase activity and inhibit the phosphorylated Ezrin (phospho-Ezrin), which was highly expressed in metastatic tumors, and then reduce the motility and invasion of cancer cells (Tang et al., 2009). Besides, berberine could inhibit cancer cell migration through blocking the PKC-mediated signaling

pathway (Lin et al., 2008), inhibit primary acute myeloid leukemia (AML) cells and leukemic stem cells (LSCs) migration via down-regulating SDF-1 protein (Li et al., 2008), and suppress melanoma cancer cell migration by inhibiting the expressions of COX-2, prostaglandin E (PGE)2 and PGE2 receptors (Singh et al., 2011).

In other ways, berberine could enhance the radiosensitivity of cancer cells (Liu et al., 2011; Peng et al., 2008). In Hela cells transfected with connexin-32, it could potentize cell apoptosis induced by X-rays irradiation, probably through the enhancement of gap junction intercellular communication (GJIC) (Liu et al., 2011). Therefore, the anti-cancer effect of berberine is mainly involved in the regulation of cancer cell growth, death and metastasis. In the future, it is necessary to verify its anti-cancer effect from bench to bed.

5.4. Cardiovascular Protective Effect of Berberine

Many studies reported berberine could protect heart and vascular systems. On the one hand, it could alleviate cardiotoxicity, improve cardiac dysfunction and arrhythmia. On the other hand, it was able to fight against atherosclerosis due to its protective actions, such as inhibiting oxidative stress and vascular inflammation, ameliorating endothelial dysfunction, suppressing vascular smooth muscle cell (VSMC) proliferation and migration, and inhibiting foam cell formation and lipid accumulation.

5.4.1. Cardioprotective Effect

In vitro and in vivo studies, berberine was reported to have a potential protective role in heart. In cultured neonatal rodent cardiomyocytes, it was found to be a muscarinic agonist at M2 receptors and could reduce the contraction rate of cardiomyocytes (Salehi and Filtz, 2011). In a cardiotoxicity mice model, berberine could attenuate the myocardial injury induced by doxorubicin (Zhao et al., 2011). Similarly, it could improve LPS-induced cardiac dysfunction in rats (Yang et al., 2006). It was also able to ameliorate cardiac dysfunction in hyperglycemic and hypercholesterolemic rats through decreasing cardiac lipid accumulation and increasing glucose transport (Dong et al., 2011). In mice, pre-treatment with berberine could significantly reduced LPS-induced cardiac dysfunction via inhibiting myocardial apoptosis, cardiac I-κB α subnuit phosphorylation, and inflammatory factors production, such as TNF-α, IL-1β and NO (Wang et al., 2011). Besides, in the rat type 2 diabetic myocardial infarction model, berberine had an anti-arrhythmic effect, maybe via up-regulation of IK1/Kir2.1 (Wang et al., 2011).

5.4.2. Anti-atherosclerosis Effect

Atherosclerosis is a complicated pathological condition in arteries. Many risk factors are found to be associated with the pathophysiological process of atherosclerosis, such as oxidative stress and vascular inflammation, endothelial dysfunction, VSMC proliferation and migration, foam cell formation and lipid accumulation. Recently, increasing studies have found that berberine had multiply protective effects against these vascular risk factors, and could be used to prevent and treat with atherosclerosis.

First, berberine could reduce vascular oxidative damage and inflammation. In macrophage, it could significantly inhibit the expression of pro-inflammatory factors, such as TNF-α, and suppress pro-inflammatory responses through AMPK and PPAR-γ activation (Chen et al., 2008; Jeong et al., 2009). In human peripheral blood monocytes (PBMC), it could inhibit COX-2 expression via the ERK1/2 signaling pathway (Guo et al., 2008). In apoE-knockout mice, chronic administration of berberine could significantly ameliorate aortic lesions, inhibit oxidative stress and inflammatory factors, such as adhesion molecules, in aorta (Wang et al., 2011). Second, it could improve endothelial function. In both cultured endothelial cells and blood vessels isolated from rat aorta, berberine could protect against endothelial injury and enhance the endothelium-dependent vasodilatation partly through the activation of the AMPK pathway (Wang et al., 2009). It was also able to up-regulate and mobilize circulating endothelial progenitor cells, as well as improve small artery elasticity in healthy people (Xu et al., 2008 & 2009). Third, it could attenuate the proliferation and migration of VSMCs. In a VSMC cell line (A7r5), berberine could inhibit cell proliferation through inducing cell cycle arrest (Liu et al., 2011). It could also inhibit platelet-derived growth factor (PDGF)-induced VSMC growth and migration via activation of AMPK/p53/p21 (Cip1) signaling and inhibition of Rac1 and Cdc42, respectively (Liang et al., 2008). Fianlly, it could inhibit foam cell formation and promote cholesterol efflux. In oxidized low-density lipoprotein (ox-LDL) pre-treated macrophage, berberine could abrogate the formation of foam cells from macrophage, and reduce lipid accumulation in macrophage via promoting LXRα-ABCA1-dependent cholesterol efflux (Lee et al., 2010). Another research found berberine could inhibit the expression of nectin-like ox-LDL receptor-1 (LOX-1) and enhance the expression of SR class B type I (SR-BI) in macrophage-derived foam cells (Guan et al., 2010), which indicated that berberine might also promote cholesterol efflux via SR-BI. However, berberine was also reported to promote in vivo foam cell formation and atherosclerosis development in apoE-knockout mice (Li et al., 2009). This contradiction may be due to the different experimental models used and further researches are needed to investigate its in vivo effect.

5.5. Anti-diabetic Effect of Berberine

There are two types of diabetes mellitus, in which type 1 diabetes is featured with islet damage and lack of insulin, while type 2 diabetes is a chronic metabolic disease with the characteristics of insulin resistance, hyperglycemia, hyperlipidemia, and severe complications, such as vascular and nephritic injure. Berberine has recently been shown to have protective efficacy in both two type diabetes because of its actions on the protection of islet cells and regulation of glucose, lipid and insulin metabolism.

5.5.1. Improvement of Insulin Resistance

Insulin resistance plays a central role in the pathogenesis of type 2 diabetes. In the first place, berberine could alleviate insulin resistance. In insulin-resistant muscle cells, berberine could overcome insulin resistance, and the mechanisms involved in regulating insulin signaling pathway and reducing PPARγ and FAT/CD36 expressions (Chen et al., 2009; Liu et al., 2010). In 3T3-L1 adipocytes, berberine could reverse free-fatty-acid-induced insulin resistance through inhibiting IKKβ

phosphorylation (Yi et al., 2008). In Diabetic Hamsters, Berberine could improve fat-induced visceral white adipose tissue insulin resistance through increasing visceral white adipose tissue liver X receptors (LXRs) and peroxisome proliferator-activated receptors (PPARs) expression, while decreasing sterol regulatory element-binding proteins (SREBPs) expression (Li et al., 2011; Liu et al., 2010). In high-fat-fed rats, berberine was able to improve insulin-resistant status at least partly via AMPK activation (Lee et al., 2006). In the second place, it could increase insulin sensitivity and secretion. Berberine could increase insulin secretion probably by increasing GLP-1 secretion, which is an insulinotropic gut hormone released from intestinal L cells (Yu et al., 2010). In a rat pancreatic beta cell line, it could increase glucose-stimulated insulin secretion (GSIS), probably as an agonist of fatty acid receptor GPR40, which can enhance GSIS (Rayasam et al., 2010). In 3T3-L1 fibroblasts and Min6 cells, it could act as an effective insulin sensitizing and insulinotropic agent through activation of insulin/insulin-like growth factor-1 signaling cascade (Ko et al., 2005). In type 2 diabetic rats, it was able to increase insulin sentivity, probably through protein kinase C-dependent up-regulation of insulin receptor expression (Kong et al., 2009; Wang et al., 2011). In primary rat islets, berberine could also enhance GSIS probably through up-regulating hepatic nuclear factor 4α (HNF4α) and glucokinase (GK) activity (Wang et al., 2008).

5.5.2. Hypoglycemic Effect

High blood glucose is the main feature of diabetes, and can cause severe diabetic complications. In vitro and in vivo studies, as well as clinical trials have found berberine could lower hyperglycemia in diabetes. In alloxan-induced diabetic C57BL/6 mice, berberine could reduce blood glucose by enhancing liver glycogen synthesis, and this action was mediated through the activation of Akt signaling pathway (Xie et al., 2011). It could also enhance cell glucose uptake. In L929 fibroblast cells, it was able to activate glucose uptake through its acute activation of the transport activity of glucose transporter, GLUT1 (Cok et al., 2011). In 3T3-L1 adipocytes and L6 myocytes, it could increase glucose uptake in an insulin-independent manner (Chen et al., 2010). Besides, berbreine could improve glucose metabolism. In diabetic rats, it could lower fasting blood glucose through direct inhibiting gluconeogenesis in liver, and this activity was not dependent on insulin activity, but as a result of berberine-mediated mitochondria inhibition (Xia et al., 2011). Finally, berberine could inhibit intestinal disaccharidase activity. In diabetic rats and normal rats, berberine was able to significantly lower postprandial blood glucose level by suppressing intestinal disaccharidase and β-glucuronidase activity, and this effect was partly dependent on the activation of PKA signaling pathway (Liu et al., 2008 & 2010).

5.5.3. Hypolipidemic Effect

Hyperlipidemia is a potential risk factor for type 2 diabetes, and berberine was reported to lower blood lipids, such as free fatty acids and cholersterol. In type 2 diabetic rats, it could significantly lower blood lipids, such as low density lipoprotein-cholesterol (LDL-C) (Zhang et al., 2008). In small clinical trials, berberine might play an important role in the treatment of type 2 diabetes

via lowering blood free fatty acids, such as triglyceride, total cholesterol and LDL-C (Zhang et al., 2008; Gu et al., 2010).

5.5.4. Amelioration of Diabetic Complications

Diabetes is accompanied with multiply complications, such as microvascular injure, diabetic nephropathy and memory impairment. Berberine was reported to alleviate diabetic microendothelial injury in vitro (Hao et al., 2011). Similarly, it could ameliorate endothelial dysfunction in diabetic rats by enhancing NO bioavailability (Wang et al., 2009). It could also improve diabetes-induced renal damage. In high glucose-induced rat glomerular mesangial cells, it was able to inhibit aldose reductase, oxidative stress, as well as fibronectin and collagen accumulation (Liu et al., 2008 & 2009). In streptozotocin-induced diabetic rats, could also alleviate rat renal injury by suppression of both oxidative stress and aldose reductase (Liu et al., 2008). In diabetic C57BL/6 mice, it was able to alleviate renal injury by reducing blood urea nitrogen, serum creatinine and 24-h albuminuria (Lan et al., 2010). Besides, berberine could improve memory dysfunction in diabetic rats due to its protection of cholinergic and antioxidant system (Bhutada et al., 2011).

5.5.5. Protection of Islets

The damage of islets is mainly involved in type 1 diabetes. Berberine was able to protect islet cells from injure. In HIT-T15 pancreatic β cells, it could reduce palmitate-induced β cell lipoapoptosis probably via up-regulating PPARγ expression (Gao et al., 2011). In nonobese diabetic mice, berberine supplementation could significantly increase the number of decreased islets, and ameliorate insulin and blood lipids status (Chueh and Lin, 2011). In type 1 diabetic mice, it could inhibit T cell-mediated destruction of islet β cells and severe islet inflammation through suppressing Th17 and Th1 differentiation (Cui et al., 2009). In diabetic rats, it could also increase islet β cell regeneration, antioxidant enzyme activity and decrease lipid peroxidation, therefore protect islets from oxidative damage (Zhou et al., 2009).

5.6. Neuroprotective Effect of Berberine

It has been confirmed that berberine could enter into the central nervous system (Wang et al., 2005), and it's the prerequisite for its neuroprotective effect. Studies found it could fight against many nervous system diseases, such as neurodegenerative diseases and neuronal injure. Berberine was reported to combat against neurodegenerative diseases, especially Alzheimer's disease (AD). AD is featured with amyloid β (Aβ) aggregation, tau hyperphosphorylation and neuron death. Berberine could fight against Aβ. In vitro experiments, berberine and its derivatives were found to inhibit Aβ aggregation and the activity of acetylcholinesterase (AchE) (Habtemariam, 2011; Shan et al., 2011). In cultured rat cortical neurons, it could inhibit Aβ-induced cell toxicity by increasing cell viability and inhibiting cell apoptosis (Wang et al., 2011). It could also reduce Aβ secretion by modulating the process of Aβ production (Asai et al., 2007). In addition, it was able to inhibit tau hyperphosphorylation. In HEK293 cells transfected with tau, it could significantly reduce calyculin A-induced tau hyperphosphorylation, probably through restoring protein phosphatase 2A activity and

inhibiting glycogen synthase kinase-3β (GSK-3β) activation (Yu et al., 2011). Besides, in an AD rat model, berberine chloride could ameliorate rat spatial memory impairment (Zhu and Qian, 2006). Berberine also had a protective effect on different kinds of neuronal injure. It could alleviate toxic-induced neuronal injure. In aluminum and ibotenic acid-induced rat neuronal damage models, it could attenuate brain injury, improve the learning and memory ability impairment, inhibit neuron death and promote neuron survival and differentiation (Lim et al., 2008; Zhang et al., 2009). It could also inhibit neuro-inflammation. It could reduce the release of inflammatory factors and neurotoxic molecules from activated microglia and inhibit neuro-inflammation response (Lu et al., 2010; Nam et al., 2010). In experimental autoimmune encephalomyelitis (EAE) mice, it was able to effectively attenuate clinical and pathological parameters of EAE, reduce the permeability of blood-brain barrier, decrease the expression and activity of MMP-9, and inhibit the inflammatory infiltration (Ma et al., 2010). In addition, it could protect brain from hypoxic and ischemic injury. In ischemic-induced mouse organotypic hippocampal slice culture model, it could inhibit ischemic damage, at least partly mediated by suppression of Bcl-2 phosphorylation (Cui et al., 2009). In ischemic-hypoxic-induced rat pup brain, it could significantly reduce the brain injury and edema (Benaissa et al., 2009). Decreasing the intracellular ROS level and subsequently inhibiting mitochondrial apoptotic pathway was reported to be the main mechanism of berberine-mediated protection of ischemic brain injury (Zhou et al., 2008).

Otherwise, berberine was able to inhibit ethanol withdrawal-induced hyperexcitability and ethanol-induced rewarding effect in mice (Bhutada et al., 2010 & 2011). It could also inhibit morphine and cocaine-induced locomotor sensitization through reducing dopamine biosynthesis, dopamine receptor and N-methyl-D-aspartate (NMDA) receptor activities and post-synaptic neuronal activity (Lee et al., 2009; Yoo et al., 2006).

5.7. Anti-obesity Effect of Berberine

It has been reported that berberine had an effect on obesity. It could inhibit adipogenesis. In differentiating 3T3-L1 preadipocytes and mature adipocytes, it could inhibit adipogenesis, with the mechanisms of inhibiting adipogenic enzymes, such as fatty acid synthase, acetyl-CoA carboxylase and acyl-CoA synthase, SREBP-1, C/EBPα and PPARγ (Choi et al., 2006; Hu et al., 2010; Pham et al., 2011). Similarly, in high-fat diet-induced obesity mice, it could reduce mouse food intake and weight, probably through inhibiting the expression of PPARγ while increasing the expression of GATA-3 (Hu and Davies, 2010). It could also inhibit pre-adipocyte differentiation. In mouse preadipocyte 3T3-L1, it was able to inhibit pre-adipocyte differentiating into muture adipocyte by up-regulating both GATA binding protein 2 and 3 (GATA-2 and GATA-3), while down-regulating PPARγ and α (Hu and Davies, 2009; Huang et al., 2006). Besides, in obese mice, berberine treatment could significantly lower both body and visceral adipose weights, probably through gut microbes-mediated decreasing the degradation of dietary polysaccharides and lowering potential calorie intake (Xie et al., 2011).

5.8. Hepatoprotective Effect of Berberine

Berberine was reported to ameliorate nonalcoholic fatty liver disease (NAFLD). In NAFLD rats, it could improve the recovery of hepatic steatosis and lipid metabolism disorder, and reduce

inflammation and insulin resistance, with the mechanism of up-regulation of insulin receptor substrate-2 (IRS-2) and down-regulation of uncoupling protein-2 (UCP2) (Xing et al., 2011; Yang et al., 2011). Berberine might also be effective to alcoholic liver disease (ALD). In HepG2 cells, it could inhibit acetaldehyde, the metabolic product of ethanol, induced production of pro-inflammatory factors, such as IL-1β and TNF-α, probably through NF-κB signaling pathway (Hsiang et al., 2005). In addition, berberine could inhibit liver fibrosis. In liver fibrosis rodent models, it could protect experimental liver fibrosis through enhancing anti-oxidant system, inhibiting lipid peroxidation and hepatic stellate cell proliferation (Sun et al., 2009; Zhang et al., 2008).

5.9. Gastrointestinal Protective Effect of Berberine

Berberine has been used to treat gastrointestinal disorders for a long time. Recent studies found it could protect gastrointestinal tract from injure, and was effective to multiply gastrointestinal diseases, such as ulcerative colitis. Firstly, it could ameliorate gastrointestinal inflammation. In ethanol-induced gastric ulcer mice model, it could significantly protect ethanol-induced gastric mucosa damage, probably by increasing the expression of eNOS while inhibiting the expression of iNOS (Pan et al., 2005). In lipopolysaccharides (LPS)-induced rat and mouse intestinal injury, it could inhibit intestinal inflammation, such as inhibition of COX-2 expreesion, enterocyte apoptosis, neutrophil infiltration, and therefore alleviate intestinal damage, probably through increasing the activities SOD and glutathione peroxidase (GSH-Px), inhibiting TLR4-NF-κB and p38-PPAR-γ signaling pathways (Feng et al., 2011; Li et al., 2011; Zhang et al., 2011). In 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced mice colitis, it could improve colitis via inhibiting lipid peroxidation, enterobacterial growth and NF-κB activation (Lee et al., 2010). In indomethacin (IND)-induced mouse small intestinal injure, it could prevent IND-induced enteropathy and reduce the incidence of mice lethality by decreasing the elevation of adenosine via inhibiting adenosine deaminase (ADA), a key enzyme of adenosine catabolism (Watanabe-Fukuda et al., 2009). Secondly, it could inhibit intestinal epithelial barrier damage. In vitro model of intestinal epithelial cell (Caco-2) monolayers, it could increase tight junction integrity by measuring transepithelial electrical resistance (TEER), and attenuate TNF-α and IFN-γ-induced barrier penetration via inhibiting the dislocation of tight junction protein occludin from raft fractions to non-raft fractions in membrane microdomains (Gu et al., 2009; Ning et al., 2010). It could also antagonize TNF-α-mediated barrier defects in HT-29/B6 human colon monolayers and rat colon, through preventing TNF-α-induced claudin-1 disassembly and upregulation of claudin-2 (Amasheh et al., 2010). In a mouse model of endotoxinemia, it could attenuate the disruption of tight junctions in intestinal epithelium, probably mediated by inhibiting NF-κB and myosin light chain kinase pathway (Gu et al., 2011). In addition, berberine could inhibit radiation-induced intestinal injure. In mice undergoing abdominal radiotherapy, it could attenuate mice intestinal injury and delay mice mortality (Li et al., 2010). In a small clinical trial, it could significantly decrease the incidence and severity of radiation-induced acute intestinal symptoms (RIAISs), and postpone the occurrence of RIAIS in patients with abdominal or whole pelvic radiation (Li et al., 2010).

5. 10. Anti-rheumatic Effect of Berberine

Rheumatic diseases, such as rheumatoid arthritis (RA) and osteoarthritis, are a series of inflammatory disorders mainly affecting joints and connective tissue. Berberine was found to be effective to rheumatic diseases due to its important bioactive abilities, such as anti-inflammatory ability. It was reported to ameliorate rheumatic arthritis. Activated rheumatoid arthritis fibroblast-like synoviocytes (RAFLSs) play a vital role in the initiation and progression of RA, and berberine could inhibit RAFLS proliferation and increasing RAFLS apoptosis, probably through induction of cell cycle arrest at the G0/G1 phase and regulation of apoptosis mediators, respectively (Wang et al., 2011). It could also alleviate osteoarthritis. In rabbit articular chondrocytes and experimental rat osteoarthritis model, it could inhibit IL-1β-induced release of collagen, proteoglycan, glycosaminoglycan (GAG) and NO, as well as down-regulate MMPs and up-regulate tissue inhibitor of metalloproteinase (TIMP-1) (Hu et al., 2011; Moon et al., 2011). In osteoblastic cells, it could promote osteoblast differentiation by Runx2 activation through p38 MAPK signaling pathway (Lee et al., 2008). Meanwhile, it could inhibit osteoclast formation and survival via suppression of NF-κB and Akt activation (Hu et al., 2008). In glucocorticoid-induced osteoporosis rats, it could inhibit bone resorption while improve bone formation (Xu et al., 2010). Therefore, it may have a therapeutic potential for the treatment of cartilage damage in osteoarthritis.

5.11. Other Bioactivities of Berberine

Except what discussed above, berberine has many other bioactivities and pharmacological effects (Table 2), such as anti-angiogenic and anti-clastogenic effects.

Table 2. Other Bioactivities of Berberine

Bioactivites	Mechanisms	References
Anti-angiogenic effect	Inhibition of HIF, VEGF, MMP2, and pro-inflammatory factors	Gao et al., 2009; Hamsa and Kuttan, 2012; Jie et al., 2011
Anti-clastogenic effect	Inhibition of lipid peroxidation and modulation of phase I and II detoxification cascade.	Sindhu and Manoharan, 2010
Anti-convulsant effect	Modulation of neurotransmitter systems	Bhutada et al., 2010
Anti-depressant effect	Modulation of brain biogenic amines via NO-cGMP signaling pathway	Kulkarni and Dhir, 2007 & 2008; Peng et al., 2007
Anti-diarrhea effect	Reduction of epithelial gut permeability	Gu et al., 2009
Anti-skin aging effect	Prevention of skin inflammation and the degradation of extracellular matrix proteins	Kim and Chung, 2008; Kim et al., 2008
Anti-uveitis effect	Inhibition of inflammatory mediators, such as MCP-1, CINC-1 and IL-8	Cui et al., 2006 & 2007
Muscle-relaxing effect	Inhibition of muscarinic acetylcholine receptors	Sanchez-Mendoza et al., 2008

cGMP: cyclic guanosine monophosphate; CINC-1: cytokine- induced neutrophil chemoattractant-1; HIF: hypoxia-inducible factor; IL-8: interleukin-8; MCP-1: monocyte chemotactic protein 1; MMP2: matrix metalloproteinase 2; VEGF: vascular endothelial growth factor.

6. Conclusions and Prospects

Although berberine-containing medicinal plants have been used for a long time in traditional medicines, berberine has just attracted increasing research interest in recent years due to its various significant bioactivities. This review mainly summarized recent studies on its natural sources, separation and detection methods, absorption and metabolism, as well as bioactivities, which were specially emphasized. However, most studies on its beneficial effects were based on cell and animal disease models, the effects of berberine on human diseases remain largely uncertain. Therefore, in the future, clinical trials are appreciated to verify the beneficial effects of berberine on human. Besides, this already accumulated evidence can also provide important theoretical basis for its clinical application in the future.

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