A review on pharmacological effects of *Rhizoma Coptidis* (Huang lian)

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ABSTRACT

Huang Lian (*Rhizoma coptidis*, *RC*), which has effects on clearing damp-heat, quenching fie, and counteracting poison, is a herb frequently used in many traditional formulas. At present, there are many researches on the pharmacological effects of *RC*. In this review, we summarize the research progress on pharmacological effects of RC from four main aspects, in order to guide clinical application and explore the prospects of the application of *RC*.

KEY WORDS: *Rhizoma Coptidis*; Pharmacology; Research progress

Rhizoma Coptidis is the dry rhizome of ranunculaceae coptis from Sichuan Province, Hubei Province, Guizhou Province, and Shanxi Province in China. It is listed as "the top grade" in the earliest traditional Chinese medicine monograph Sheng Nong's Herbal Classic, and is a plant alkaloid that is used in Chinese medicine. In the primary part of the Chinese pharmacopeia 2010, there are three cultivated varieties of *RC* including C. Chinensis Franch, C. deltoidea, C.Y. Cheng et Hsiao and C. teeta Wall. *RC* is a herb of bitter flavor and cold property, entering channels of heart, spleen, stomach, gallbladder, and large intestine. It has effects of clearing damp-heat, quenching fie, and counteracting poison. In this review, we summarize the research progress on the pharmacological effects of *RC* from four main aspects of contents, including its anti-microorganism function, effects on metabolic diseases, angiocardiopathy and cerebrovascular disease, gastrointestinal tract in both English and Chinese search engines, in order to guide clinician to use *RC* moresuitably and reasonably in the clinical practice.

ANTI-MICROORGANISM FUNCTION

Antibacterial and antiviral effects of RC

As a herb, antimicrobial and antiprotozoal effects of *RC* were traditionally used in Ayurvedic, Chinese and Middle-Eastern folk medicine. In Ayurveda, berberine (BBR) extractsand decoction were demonstrated to have significant antimicrobial effects against a variety of organisms including bacteria, virus, fungi, protozoa, helminthes and Chlamydia[1]. In traditional Chinese medicine (TCM), *RC* was used for treating bacterial diarrhea due to its antimicrobial, antiprotozoal, and antidiarrheal activity for a long history. BBR, an isoquinoline alkaloid, is the major active component of *RC*. It was previously reported that *RC* and BBR all had significant antibacterial and antiviral action, with broad antimicrobial spectrum, such as the gram positive and negative bacteria, the total influenza virus and fungi,[2] Yan, et al[3]. found that the three kinds of BBR alkaloids of *RC* (berberine, palmatine, jatrorrhizine) have inhibitory effects on the growth and metabolism of Staphylococcus aureus. This biothermo kinetic process can be objectively showed by parameters of thermal spectrum curve, the growth rate const, gross calorie and thetime to peak. The greater of the growth rate const, the shorter of time to peak, all can prove weak antibacterial activity and vice versa subsequently. Different doses of BBR on helicobacter pylori (HP) showed a certain inhibitory effect, especially 250μg of BBR showed optimal antibacterial activity[4]. Jiang et al.found that the extracts of *RC* had strong inhibitory effect on the growth of the two periodontal pathogens, which indicated that *RC* could be used in the treatment of periodontitis[5]. BBR had a certain activity of defending a variety of pathogenic fungi, including plant fungal pathogens, et al. Also, it had significantly inhibitory effects on Candida albicans and Cryptococcus histolyticus, which was sensitive to Cryptococcus histolyticus[6]. Moreover, *RC*, an antiviral herb, can kill a lot of virus, such as Coxsackie virus, Influenza virus, Rubella virus, Herpes simplex virus et al. In recent years, Ma et al.[7] pointed out that the aqueous extract solution had strong inhibitory effect on infectivity of influenza A virus (IAV), probablydue to the inhibition on RNA polymerase of viruses. In summary, *RC* and BBR had been demonstrated to be antibiotic and antivirotic.

Anti-endotoxin effect of RC

Many studies have indicated that BBR have significant protective effect on defending endotoxic. Qian et al.[8] investigated the mechanism by which BBR and crude extract (CE) of *RC* reduced endotoxemia in the rats. The results showed that both BBR and CE of *RC* could relieve symptoms effectively, but CE worked better, which may because of a small amount of other substances such as coptisine and palmatine. BBR remarkably decreased mortality and

attenuated tissue injury of lung, liver, kidneys and small intestine in mice challenged with LPS, which may be related to its decreasing plasma TNF-a, IFN-γ and NO levels and increasing plasma IL-10 level during endotoxemia. These findings provide a new strategy for the treatment of endotoxemia[9].

METABOLIC DISEASES

Effects of RC on type 2 diabetes mellitus (T2DM) and its complications

Effects of RC on DM

TCM is showing a bright future in the treatment of T2DM. TCM treatment has certain advantages of less toxicity and/or side effects, and herbs could provide multiple therapeutic effects. *RC* is widely used in the treatment of T2DM. *RC* extracts and related formula may be more effective than its single alkaloid. Numerous scientific researches have showed definite hypoglycemic effects of *RC* and BBR, the mechanism was complex, which may included improvement of insulin sensitivity, promotion of insulin secretion, regulation of glucose and lipid metabolism in liver, inhibition of intestinal absorption of glucose, and development of antioxidant activities aimed at diabetic complications[10-19]. Wang et al.[20] have proved that BBR had a better hypoglycemic activity compared with metformin.In addition, BBR could alleviate diabetic complications, cardiovascular and cerebrovascular damage, nervous system damage, kidney damage and so on. Wu et al.[21] observed efficacy of BBR on treating T2DM. Seventy-two cases were assigned to obese group and non-obese group; BBR (0.02mg/kg) was administrated orally for 8 to 10 weeks. Results indicated that insulin resistance and body mass index (BMI) of all cases improved after treatment (P<0.01). BMI of obese group reduced more significantly than that of non-obese group (P<0.01), showing that BBR was more applicable to prediabetes and the early stage of T2DM characterized by insulin resistance and obesity. We need more researches for BBR was merely the component of RC and did not represent *RC* totally. The review above showed that *RC* could be effective in improving the glucolipid metabolism. The modern pharmacological researches on RC are actually developing and more and more scientific evidence s are provided and reported.

Effects of RC on diabetes complications

Diabetic nephropathy (DN): Diabetic nephropathy is one of the most severe microvascular complications of DM. In recent years, many studies have indicated that *RC* can be used to treat DN. Ming et al.[22] observed the curative effect of BBR on DN in meta-analysis and found that BBR had a comprehensive treatment of DN in many ways, such as reducing the blood sugar, lowering cholesterol, lowing C-reactive protein and reducing vascular damage,to achieve the goal of the treatment of DN finally. Liu et al.[23] found that BBR ameliorated renalinjury in streptozotocin-induced Wistar rats by inhibitingaldose reductase and oxidative stress. After the treatment with oral administration of BBR (200mg/kg/d), fasting blood glucose (FBG), blood urea nitrogen (BUN), serum creatinine (Cr), and 24hurinary albumin(24h-UAlb)were significantly decreased, and serum superoxide dismutase (SOD) activity was increased, while the contentof malondialdehyde (MDA), aldose reductase (AR) activity, and the expressionof AR mRNA and protein in the kidney were markedly decreased compared with that of the control group (P<0.05).

Diabetic peripheral neuropathy (DPN): Diabetic peripheral neuropathy iscommon in diabetic complications. BBR has shown positive effect in treating DPN. Hyperglycemia can induce neuronal apoptosis, contract the growth cone and inhibit the growth of the nerve axons[24], which finally leads to DPN. Many studies showed that BBR can relieve the symptoms of DPN, mainly through reversing the nerve conduction velocity caused by high blood sugar and relieving the sense of cold, heat and mechanical pain sensitivity in acute and subacute DPN[25, 26].

Effects of RC onlipid metabolism

At present, it has been proved that BBR has a definite therapeutic effect on modulating blood lipids in clinical practice[27,28]. BBR showed definite effects on lowering the levels of total cholesterol (CHO), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C), which had been observedin clinical and basic researches[29]. Kong et al. [30-32] found that BBR up-regulated the expression of hepatic low-density lipoprotein receptor (LDLR), which was mainly dependent on stabilizing LDLR message ribonucleic acid mRNA in an extracellular signal-regulated kinase (ERK) pathway. In addition, the protective effect of BBR on the liver may be an important mechanism of reducing blood lipids.

Effects of RC on blood pressure

RC has been used for lowering blood pressure for a long time. The blood pressure-lowering activity of *RC* has been confirmed by several clinical trials. Fu et al.[33] investigated the efficacy of BBR in a pilot study; 38 adults with hypertension were randomly assigned to BBR (400-600mg three times a day) in the 4-month study. Results showed that BBR significantly lowered blood pressure,systolic pressure decreased from (21.9±2.3) kPa to (18.2±1.9)kPa (P<0.01),diastolic pressure decreased from (13.6±1.6) kPa to (11.4±1.2) kPa (P<0.05). BBR can reduce

blood pressure through loosing aorta, inhibiting activity of cholinesterase, etc. Always there are dose differences and individual differences in clinical research. The antihypertensive effect on individual patient is not significant until the dosage of *RC* reached to 1.59g/d, but some patients (mainly in patients with systolic blood pressure elevation) will appear mild hypotension reaction by only taking 0.99g/d *RC*[34,35].

EFFECTS OF *RC* ONCARDIOCEREBRAL VASCULAR DISEASES

RC was used for improving the acute cerebral ischemia and cerebral hypoxia in the treatment of cardiovascular disease, such as arrhythmia, heart failure and myocarditis.Wang et al.[36] conducted a research on the effect of BBR on experimental arrhythmia. The results showed that BBR in high dose (240mg/kg) could reduce the risk of ventricular fibrillation to 40%, and the time of ventricular fibrillation was significantly shortened than before. The study showed a good antagonism against the rapid ventricular arrhythmia of it. *RC* can protect myocardial ischemi (cell); its mechanism may be related to stabilization of the cellular membrane structure, improvement of the antioxidant ability of myocardium, reduction of the occurrence of inflammatory reaction and reducing myocardial enzymes' release[37]. Xu et al.[38] found that different doses of the Huanglian Jie Du decoction could significantly prolong the survival time of mice with ligation of bilateral common carotid arteries. RC has a certain effect on anti-cerebral ischemia and anoxia.

EFFECTS OF *RC* ONGASTROINTESTINAL TRACT

Effects of BBR on modulating gut microbiota

BBR possesses significant antimicrobial activity, which maybe related to its antidiabetic mechanism. Bacteroidetes and Firmicutes were two types of gut microbiota that affect energy metabolism homeostasis, and some studies suggested that obese humans or animals have more Firmicutes and less Bacteroidetes than lean couples controls[39,40]. Xie et al.[41] investigated effects of BBR on gut microbes in high-fat diet-fed (HFD) mice. Results showed that BBR significantly lowered the levels of blood glucose and lipids. Moreover, BBR significantly reduced the number of Firmicutes and increased that of Bacteroidetes in the feces of HFD-fed mice. BBR was shown to enrich SCFA-producing bacteria; the beneficial effects of SCFAs included improving gut barrier functions, alleviating inflmmation, or creating a nonpermissive environment for pathogens, which may also help to improve obesity and insulin resistance-related metabolic abnormalities.

Effects of RC on diarrhea

Chen et al.[42] considered the effect of BBR was characterized in murine models mimicking diarrhea-predominant irritable bowel syndrome (IBS-D) symptoms. In mouse models, BBR prolonged GI transit and time to diarrhea in a dose-dependent manner, and significantly reduced visceral pain. In physiological conditions the effects of BBR were mediated by mu-(MOR) and delta-(DOR) opioid receptors; hypermotility, excessive secretion and nociception were reversed by BBR through MOR and DOR-dependent action. BBR significantly relieved IBS-D symptoms in animal models, possibly through mu- and delta-opioid receptors. BBR may become a new drug candidate for the successful treatment of IBS-D in clinical conditions.

SUMMARY AND OUTLOOK

RC is a commonly used herb for the treatment of many diseases. BBR, consistent with *RC*, possesses bitter flavor and cold property. It is a classical component that is commonly used for treating inflammation, T2DM and its complications, thus arousing strong interests in different ways. With increasing incidence of obesity, metabolic disease and cardiovascular diseases, it is likely to become more prevalent in the future. Therefore, more high-quality researches are necessary. In this review, we provided scientific evidence about the pharmacological action of *RC*, in order to provide better clinical application and to explore the prospects of the application of *RC*. It will bring great benefits to further researches on expanding its effects on broad distribution, simple cultivation and rich resource. Also, it will be predicted to be widely exploited in the near future.

REFERENCES

1 M.S. Arayne, N.Sultana, S.S.Bahadur, et al. "The berberis story: Berberis vulgaris in therapeutics". Pak J Pharm Sci, 2007(20):83-92.

2 C.J.Zhang. "Summary of research progress on pharmacological action of Rhizoma". Technology Innovation and Application, 2013(5):101.

3 Yan D.Yan, Xiao X.H.Xiao, Jin C, et al. Jin and X.P.Dong, "Effect of microcalorimetricstudy of berberine alkaloids on growth and metabolism of Staphylococcus aureus." Science in China (Series B: Chemistry),2008:487-491.

4 Yang X.T.Yang, Wang Z.R.Wang, Wang Z.J.Wang, et

al.Z.J.Liu and L.Zhang "Antimicrobial activity of berberine against Helicobacter pylori *in vitro*". Journal of TongJi university (medical science), 2014, 35(6):63-66,112.

5 Jiang G.S., Wu Jiang,Q.Z.Wu."Inhibitory effect of extracts from Rhizoma chinensis on periodontal pathogens". Shandong Medical Journal,2000,40(18):41.

6 Wu L. Wu,"Research Progress on antifungal activity of Berberine". Technology Innovation and Application,2015(24):73.

7 Ma W.L.Ma,Luo F.Luo, Li J.Y.Li, et al. "Effect of Coptis chinensis aqueous extract on activity of influenza A virus". Journal of Guangdong Medical College,2014(6):759-762.

8 Zhang Q.Zhang,Piao X.S.Piao,Lu T,.Lu et al. "Extract of Rhizoma chinensis to alleviate intestinal injury induced by endotoxin in rats". 2009 Academic annual conference proceedings of Chinese Association of Animal Science and Veterinary Medicine(Volume II),2009:1.

9 Li F.Li, Mechanisms for a decrease in mortality of endotoxemic mice by berberine. Ji'nan:Ji'nan University,2005.

10 G. Derosa, P. Maffii, and A. F. G. Cicero. "Berberine on metabolic and cardiovascular risk factors: an analysis from preclinical evidences to clinical trials". Expert Opinion on Biological Thrapy,2012,12(8):1113-1124.

11 I. P. Singh and S. Mahajan. "Berberine and its derivatives: a patent review (2009–2012)." Expert Opinion on Thrapeutic Patents,2013:215-231.

12 P. R. Vuddanda, S. Chakraborty, and S. Singh. "Berberine:a potential phytochemical with multispectrum therapeutic activities." Expert Opinion on Investigational Drugs, 2010,19(10):1297-1307.

13 Q. Zhang, X. Xiao, K. Feng et al. "Berberine moderates glucose and lipid metabolism through multipathway mechanism." Evidence-Based Complementary and Alternative Medicine,2011:10.

14 W. H. Chueh and J. Y. Lin. "Protective effct of berberine on serum glucose levels in non-obese diabetic mice." International Immunopharmacology,2012,12(3):534-538.

15 Q. M. Chen and M. Z. Xie. "Studies on the hypoglycemic effct of Coptis chinensis and berberine." Acta Pharmaceutica Sinica,1986,21(6):401-406.

16 W.J. Kong, H. Zhang, D.Q. Song et al. "Berberine reduces insulin resistance through protein kinase C-dependent upregulation of insulin receptor expression." Metabolism: Clinical and Experimental,2009,1(58):109-119.

17 S. H. Kim, E.J. Shin, E.D. Kim, T. Bayaraa, S. C. Frost, and C.-K. Hyun. "Berberine activates GLUT1-mediated glucose uptake in 3T3-L1 adipocytes." Biological and Pharmaceutical Bulletin,2007,30(11),2120-2125.

18 W.H. Chueh and J.Y. Lin. "Berberine, an isoquinoline alkaloid in herbal plants, protects pancreatic islets and serum lipids in nonobese diabetic mice." Journal of Agricultural and Food Chemistry,2011,59(14):8021-8027.

19 Yang J. Yang, Yin J. Yin, Gao H. Gao,et al. L. Xu, Y. Wang, and M. Li, " Berberine improves insulin sensitivity by inhibiting fat store and adjusting adipokines profie in human preadipocytes and metabolic syndrome patients". Evidence-based Complementary and Alternative Medicine, 2012:9.

20 Wang R.Wang,Gu Y.R.Gu."Comparison of therapeutic effect of Berberine Hypoglycemic Capsules and metformin on type 2 diabetes mellitus." Study Journal of Traditional Chinese Medicine,2003,21(7):1189-1190.

21 Wu D., Wu and Wei J. Wei. "Clinical observation on berberine treating type 2 diabetes mellitus." Acta Universitatis Medicinalis Nanjing,2009,29(5):736-738.

22 Yao J.M. Yao. "Efficacy and safety of Berberine on th of Diabetic Nephropathy: meta-analysis". Ji'nan:Shandong University Of Traditional Chinese Medicine,2014.

23 Liu W.H. Liu, Hei Z.Q. Hei, Nie H. Nie,et al. "Berberine ameliorates renal injury in streptopzotocin-induced diabetic rats by suppression of both oxidative stress and aldose reductase". Chinese Medical Journal, 2008,121(8):706-712.

24 G.M.Leinninger,J.W.Russell, C.M.van Golen, et al."Insulin-like growth factor-I regulates glucose-induced mitochondrial depolarization and apoptosis in human neuroblastoma." Cell Death Differ,2004,11(8):885.

25 S.O.Kim,H.J.Kim."Berberine ameliorates cold and mechanical allodynia in a rat model of diabetic neuropathy". Journal of Medicinal Food,2013,16(6):511-517.

26 X.L.Lan,L.R.P,X.R.Gong, et al. "Influence of berberine on nerve conduction velocity in rats with type 2 diabetic neuropathy." Modern Journal of Integrated Traditional Chinese & Western Medicine,2009(2):127.

27 Li C.L.Li,Wang Y.Q. Wang. "Research Advance on Treating Hyperlipidemia of Berberine."Chinese journal of drug evaluation,2014,31(1):19-22.

28 Zhou Y.F.Zhou, Huang S.J.Huang."Clinical observation of berberine in the treatment of 60 cases of hyperlipemia". Journal of clinical rational drug use,2011,4(8A):76-77.

29 Tang L. Q. Tang, Wei W. Wei, Chen L. M,et al. Chen, and S. Liu, "Effects of berberine on diabetes induced by alloxan and a high-fat/high-cholesterol diet in rats". Journal of Ethn opharmacology,2006,108(1):109-115.

30 Kong W. Kong, Wei J. Wei, P. Abidi, et al. "Berberine is a novel cholesterollowering drug working through a unique mechanism distinct from statins". Nature Medicine,2004,10(12):1344-1351.

31 W. J. Kong, J. Liu, and J. D. Jiang. "Human low-density lipoprotein receptor gene and its regulation." Journal of Molecular Medicine (Berlin),2006,84(1):29-36.

32 P. Abidi, Zhou Y. Zhou,Jiang J.D,et al.Jiang, and J. Liu. "Extracellular signalregulated kinase-dependent stabilization of hepatic low-density lipoprotein receptor mRNA by herbal medicine berberine".Arteriosclerosis, Thombosis, and Vascular Biology,2005,25(10):2170-2176.

33 Wei Y.F.Wei,Liu H.Y.Liu. "To observe the curative effect of 38 cases of berberine in treating hypertension". Inner Mongolia Medical Journal,2000, 32(3):192-193.

34 Huang X.Y.Huang, Liu W.H.Liu. "Clinical study on the antihypertensive effect of Berberine". Modern Journal of Integrated Traditional Chinese and Western Medicine,2003,12(5).

35 Li T, Chi .Li,X.L.Chi. "Study on the clinical and mechanism of berberine in the treatment of hypertension overview". Information of traditional Chinese medicine,2003,20(4).

36 Wang C.Y.Wang,Wang G.R.,Li Wang,J.,Li et al. "Study on the effect of berberine hydrochloride on experimental arrhythmia". Chinese Journal of Gerontology,2009,29(6):651-653.

37 Liu X.T.Liu, Chen X,Jin .Chen,R.,Jin et al. "Protective Effects of Rhizoma Coptidis on Acute Myocardial Ischemia Injured Cardiomyocytes in Vivo and in Vitro". Chinese Journal of Information on Traditional Chinese Medicine, 2010,17(12):28-30.

38 Xu J.H.Xu, Yu Q.H,Cai Yu,S,.Cai et al."Effects of the Huanglian Jiedu Decoction on acute cerebral ischemia and hypoxia in mice". Journal of Shenyang Pharmaceutical University,2003,20(2):132-143.

39 R. E. Ley, P. J. Turnbaugh, S. Klein, and J. I. Gordon."Microbial ecology: human gut microbes associated with obesity." Nature,2006,444(7122):1022-1023.

40 J. K. DiBaise, H. Zhang, M. D. Crowell, R. Krajmalnik-Brown,G. A. Decker, and B. E. Rittmann."Gut microbiota and its possible relationship with obesity." Mayo Clinic Proceedings,2008,83(4):460-469.

41 Xie W. Xie, Gu D. Gu, Li J. Li, Cui K, et al. Cui, and Y. Zhang, "Effcts and action mechanisms of berberine and Rhizoma coptidis on gut microbes and obesity in high-fat diet-fed C57BL/6J mice". PLoS ONE,2011,6(9).

42 Chen C, Lu M, Pan Q, et al. Kreis M,"Berberine Improves Intestinal Motility and Visceral Pain in the Mouse Models Mimicking Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D) Symptoms in an Opioid-Receptor Dependent Manner".PLoS ONE,2015,Article ID e24520, 2011.e0145556, 2015.

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