African Journal of Pharmacy and Pharmacology Vol. 6(6), pp. 355-358, 15 February, 2012
Available online at http://www.academicjournals.org/AJPP
DOI: 10.5897/AJPP11.768
ISSN 1996-0816 © 2012 Academic Journals

Review

A combination of berberine and γ-oryzanol for hyperlipidemia therapy: An hypothesis

Yanna Pan[1], Shuai He[1], Guoping Liao[1], Lijing Chen[2] and Zhongyi Zhang[1]*

[1]Department of Pharmacy, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, PR China.
[2]Department of Pharmacy, Guangdong Women and Children's Hospital, Guangzhou, Guangdong, 510010, PR China.

Accepted 21 December, 2011

Hyperlipidemia has been thought to be a modifiable risk of coronary heart disease (CHD), and the patients generally require a chronic medication and a diet or lifestyle regulation to manage their hyperlipidemia. Meanwhile, the numbers of patients suffering from side effects are also increasing. Thus, development of novel, potent, safe and highly effective approaches to battle the world epidemics of hyperlipidemia is of crucial importance. It was reported that berberine and γ-oryzanol could reduce total plasma cholesterol (TC) and triglyceride (TG) levels and increase the high density lipoprotein cholesterol (HDL-C) level both *in vitro* and *in vivo*. Therefore, a novel hypothesis concerning the combination of berberine and γ-oryzanol for hyperlipidemia therapy is proposed. Moreover, if the poor bioavailability of berberine and γ-oryzanol can be improved, the primary hypothesis will be reasonable and feasible, and also, serve as the basis for further improvement in quality of hyperlipidemia management.

Key words: Hyperlipidemia, γ-oryzanol, berberine.

INTRODUCTION

It is well established that persistent lipid abnormalities are inversely correlated with risk for the incidence of coronary heart disease (CHD). A common form of dyslipidemia is characterized by three lipid abnormalities: elevated triglycerides, small low density lipoprotein (LDL) particles and reduced high density lipoprotein-cholesterol (HDL-C). The World Health Organization (WHO) reported that high cholesterol levels contribute to 56% of cases of coronary heart disease worldwide and causes about 4.4 million deaths each year (Kavey et al., 2003). In rural China, greater than 30% of adults older than 35 years of age have total cholesterol levels greater than 200 mg/dl. Elevated LDL (greater than 130 mg/dl) ranged from 13.8% of adult males to 17.2% of adult females. Amongst Latin American populations, the prevalence of hyper-cholesterolemia varied from 6 to 20% depending on the city. For comparison, the prevalence of elevated total cholesterol (> 240 mg/dl) in US adults from 2003 to 2006 was 16.3% (Aje and Miller, 2009).

Modeling studies suggest that lowering total serum cholesterol, either by treating elevated total serum cholesterol alone or by managing multiple risk factors, is cost-effective in many low and middle income countries (Murray et al., 2003). Generally, bile acid sequestrants, statins, fibrates and nicotinic acids are efficacious antihyperlipidaemic drugs currently available, but adverse reactions and quality of life morbidity indicates the need to find better regimens for dyslipidemia. However, in recent years, berberine (BBR) and γ-oryzanol (OZ) were described to be able to decrease plasma total cholesterol (triglyceride (TG)). Moreover, they were proven to be safe and effective through chronic clinical treatment of hyperlipidemia (Berger et al., 2005; Cecero et al., 2007), respectively. Nevertheless, we failed to find any report which showed that BBR and OZ were combined in treating hyperlipidemia. Therefore, we conduct an hypothesis: BBR and OZ, as a combination therapy protocol, can be applied in the treatment of hyperlipidemia. The combination therapy protocol plays its role in the treatment of hyperlipidemia by reducing lipid intake and regulating the metabolic of lipid (Figure 1).

*Corresponding author E-mail: zhang43499@sohu.com, panyanna0711@sina.com. Tel/Fax: +86 20 61643499.

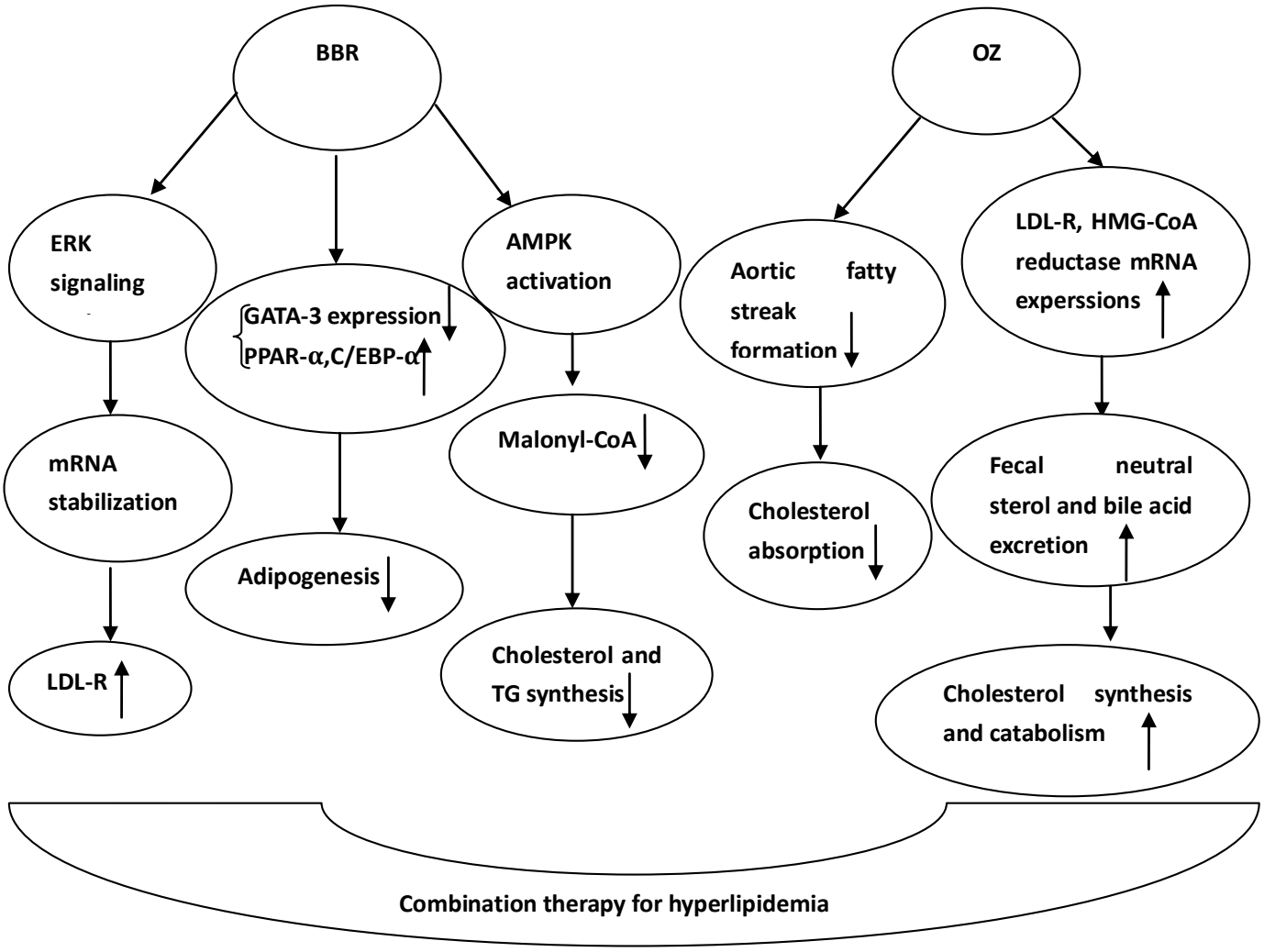

Figure 1. Principle of combination of berberine (BBR) and γ-oryzanol (OZ) for hyperlipidemia therapy.

THE EVIDENCES FOR BERBERINE IN ANTI-HYPERLIPIDEMIA

To date, berberine (Figure 2*)*, an alkaloid, has been used for thousands of years as a traditional herbal medicine to treat bacterial infection, gastro-intestinal disorders and many other illnesses, with no toxic effects reported in a body of preclinical and clinical studies (Jagetia and Baliga, 2004; Zeng et al., 2003; Ye et al., 2009; Anis et al., 2001). Recently, interest in understanding the cardiovascular protective effects of BBR appears to be mounting (Abidi et al., 2006). The cholesterol-lowering properties of BBR have been observed in human and animal studies (Cecero et al., 2007; Tang et al., 2006), with an efficacy that is comparable or greater than most of the current natural products (Jenkins et al., 2000; Vanstone et al., 2002; Wang et al., 2004) but moderate as compared to statin drugs (Rutishauser et al., 2006). The cholesterol-lowering mechanism of BBR is not yet fully elucidated. It is reported that BBR increases LDL-receptor (LDLR) expression by mRNA stabilization that is mediated by the Extracellular *signal*-regulated kinase (ERK) signaling pathway through the interactions of cis-regulatory sequences of 3'UTR mRNA binding proteins (Abidi et al., 2005) and the 5' proximal section of the LDLR mRNA 3' untranslated region responsible for the regulatory effect of BBR (Kong et al., 2004). Moreover, BBR can also up-regulates GATA-3 expression (Hu and Davies, 2010) and inhibits the mRNA and protein levels of adipogenesis related transcription factors PPAR gamma, C/EBP alpha and their upstream regulated (Huang et al., 2006).

Additionally, BBR not only activate AMP-activated protein kinase (AMPK) activator by peripheral AMPK activation, but also by neural signaling from the central nervous system (Kim et al., 2009), which decreased the level of malonyl-CoA and stimulated the expression to inhibit cholesterol and TG synthesis.

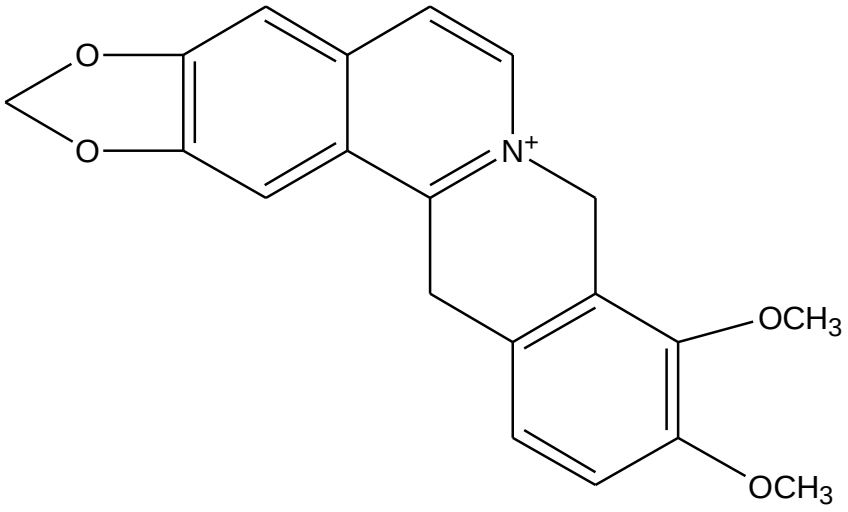

Figure 2. The chemical structure of berberine.

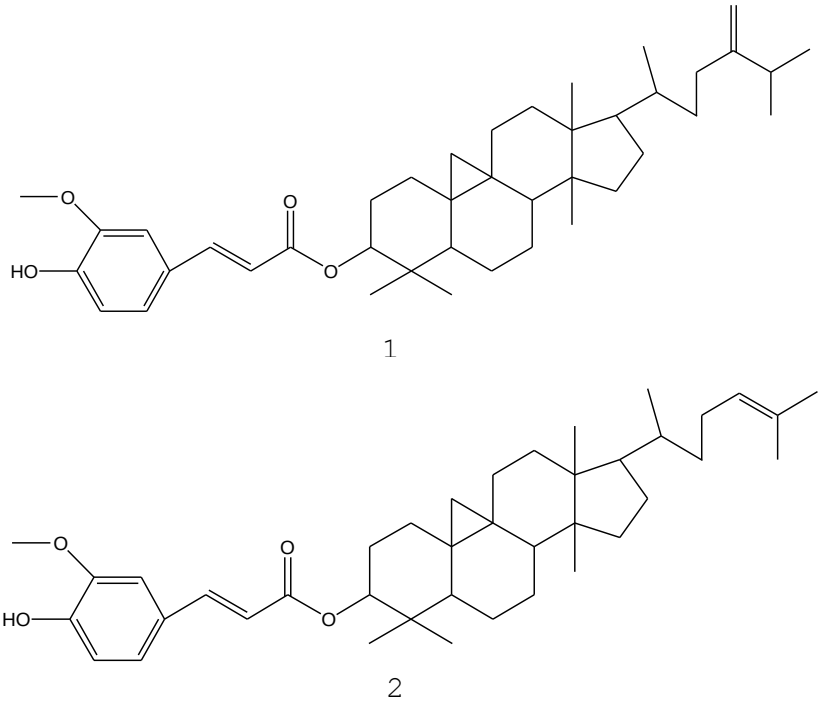

Figure 3. The chemical structures of the major components of oryzanol, compound 1: 24-Methylen-cyclo-Artanylferulate and compound 2: Cycloartenyl ferulate.

THE EVIDENCES FOR Γ-ORYZANOL IN ANTI-HYPERLIPIDEMIA

Oryzanol (OZ) is a mixture of ferulic acid esters of triterpene alcohols and primarily extracted from rice bran. 24-methylenecycloartanyl ferulate and cycloartenyl ferulate (Figure 3) have been identified as the major components, accounting for 80% of gamma-oryzanol in rice bran oil (Xu and Godber, 1999). It has been used for the treatment of menopause syndrome, neurological disorder and nerve disorders (Lerma-Garcia et al., 2009). Recently, interest in understanding the cholesterol-lowering properties of OZ appears to be mounting (Cicero and Gaddi, 2001). The cholesterol-lowering mechanism of

γ-oryzanol is not yet fully elucidated. It was reported that oryzanol has a greater effect on lowering plasma non-HDL-C levels and raising plasma HDL-C than ferulic acid in hypercholesterolemic hamsters, possibly through a greater extent to increase fecal excretion of cholesterol and its metabolites (Wilson et al., 2007) and through prevention of cholesterol absorption by reductions in aortic fatty streak formation (Rong et al., 1997). In addition, oryzanol can increase LDL-receptor and HMG-CoA reductase mRNA expressions, which lead to increased fecal neutral sterol and bile acid excretion via up-regulation of cholesterol synthesis and catabolism (Chen and Cheng, 2006). Furthermore, it is reported that oryzanol can facilitate the absorption of berberine and improve bioavailability of berberine (Li et al., 2000), which suggest a lower dosage of berberine to lower the risk of side effects.

Conclusion

Based on the aforementioned evidences, our primary hypothesis is reasonable and feasible. However, we are aware of the fact that some challenges are existing, for instance, oryzanol is insoluble in water and berberine has a poor bioavailability, indicating that their bioavailability are limited. Therefore, the limitations have to be overcome by some novel technologies or other means. More so, it is necessary to study the effects of different doses and routes of administration of the combination therapy protocol on hyperlipidemia. In a word, we do not suggest a panacea for treatment of all cases of hyper-lipidemia, but our approach to the understanding and treatment of hyperlipidemia may provide the means for intervention in many situations. It is anticipated that the hypothesis will serve as the basis for further improvement in the quality of hyperlipidemia management.

REFERENCES

Abidi P, Zhou Y, Jiang JD, Liu J (2005). Extracellular signal-regulated kinase-dependent stabilization of hepatic low-density lipoprotein receptor mRNA by herbal medicine berberine. Arterioscler. Thromb. Vasc. Biol., 25: 2170-2176.

Abidi P, Chen W, Kraemer FB, Li H, Liu J (2006). The medicinal plant goldenseal is a natural LDL-lowering agent with multiple bioactive components and new action mechanisms. J. Lipid Res., 47: 2134-2147.

Anis KV, Rajeshkumar NV, Kuttan R (2001). Inhibition of chemical carcinogenesis by berberine in rats and mice. J. Pharm. Pharmacol., 53(5): 763-8.

Berger A, Rein D, Schäfer A, Monnard I, Gremaud G, Lambelet P, Bertoli C (2005). Similar cholesterol-lowering properties of rice bran oil, with varied gamma-oryzanol, in mildly hypercholesterolemic men. Eur. J. Nutr., 44(3): 163-173.

Cicero AF, Gaddi A (2001). Rice bran oil and γ-oryzanol in the treatment of hyperlipoproteinaemias and other conditions. Phytocher. Res., 15: 277-289.

Cecero AF, Rovati LC, Setnikar I (2007). Eulipidemic effects of berberine administered alone or in combination with other natural cholesterol-lowering agents. A single-blind clinical investigation. Arzneimittelforschung, 57: 26-30.

Chen CW, Cheng HH (2006). A rice bran oil diet increases LDL-receptor and HMG-CoA reductase mRNA expressions and insulin sensitivity in rats with streptozotocin/nicotinamide-induced type 2 diabetes. J. Nutr., 136(6): 1472-1476.

Huang C, Zhang Y, Gong Z, Sheng X, Li Z, Qin Y (2006). Berberine inhibits 3T3-L1 adipocyte differentiation through the PPAR-gamma pathway. Biochem. Biophys. Res. Commun., 348(2): 571-578.

Hu Y, Davies GE (2010). Berberine inhibits adipogenesis in high-fat diet-induced obesity mice. Fitoterapia. 81: 358-366.

Jagetia GC, Baliga MS (2004). Effect of Alstonia scholaris in enhancing the anticancer activity of berberine in the Ehrlich ascites carcinoma-bearingmice. J. Med. Food, 7: 235-244.

Jenkins DJ, Axelsen M, Kendall CW, Augustin LS, Vuksan V, Smith U (2000). Dietary fibre, lente carbohydrates and the insulin-resistant diseases. Br. J. Nutr., 83(Suppl 1): S157-163.

Kavey RE, Daniels SR, Lauer RM, Atkins DL, Hayman LL, Taubert K (2003). American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. Circulation, 107(11): 1562-1566.

Kim WS, Lee YS, Cha SH, Jeong HW, Lee MR, Oh GT, Park HS, lee KU, Lane MD, Kim JB (2009). Berberine improves lipid dysregulation in obesity by controlling central and peripheral AMPK activity. Am. J. Physiol. Endocrinol. Metab., 296: E812-E819.

Kong W, Wei J, Abidi P, Lin M, Inaba S, Li C, Wang Y, Wang Z, Si S, Pan H, Wang S, Wu J, Wang Y, Li Z, Liu J, Jiang JD (2004) Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat. Med. 10(12): 1344-1351.

Lerma-Garcia MJ, Herrero-Martinez JM, Simo-Alfonso EF, et al. (2009) Composition, industrial processing and applications of rice bran γ-oryzanol. Food Chem., 115: 389-404.

Li BX, Yang BF, Hao XM, Zhou H, Sun MZ (2000). Study on the pharmacokinetics of berberine in single dosage and coadministration with oryzanol in rabbits and healthy volunteers. Chin. Pharm. J., 35(1): 33-34.

Murray CJL, Lauer JA, Hutubessy RCW, Niessen L, Tomijima N, Rodgers A (2003). Effectiveness and costs of interventions to lower systolic bold pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. Lancet, 361: 717-25.

Rong N, Ausman LM, Nicolosi RJ (1997). Oryzanol decreases cholesterol absorption and aortic fatty streaks in hamsters. Lipids, 32(3): 303-309.

Rutishauser J (2006). The role of statins in clinical medicine -LDL-cholesterol lowering and beyond. Swiss MedWkly. 136: 41-49.

Aje TO, Miller M (2009). Cardiovascular disease: A global problem extending into the developing world. World J. Cardiol., 1(1): 3-10.

Vanstone CA, Raeini-Sarjaz M, Parsons WE, Jones PJ (2002). Unesterified plant sterols and stanols lower LDL-cholesterol concentrations equivalently in hypercholesterolemic persons. Am. J. Clin. Nutr., 76: 1272-1278.

Wang Y, Jones PJ, Ausman LM, Lichtenstein AH (2004). Soy protein reduces triglyceride levels and triglyceride fatty acid fractional synthesis rate in hypercholesterolemic subjects. Atherosclerosis, 173: 269-275.

Wilson TA, Nicolosi RJ, Woolfrey B, Kritchevsky D (2007). Rice bran oil and oryzanol reduce plasma lipid and lipoprotein cholesterol concentrations and aortic cholesterol ester accumulation to a greater extent than ferulic acid in hypocholesterolemic hamsters. J. Nutr. Biochem., 18: 105-112.

Xu Z, Godber JS (1999). Purification and identification of components of γ-oryzanol in rice bran oil. J. Agric. Food Chem., 47: 2724-2728.

Ye M, Fu S, Pi R, He F (2009). Neuropharmacological and pharmacokinetic properties of berberine: a review of recent research. J. Pharm. Pharmacol., 61(7): 831-7.

Zeng XH, Zeng XJ, Li YY (2003). Efficacy and safety of berberine for congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am. J. Cardiol., 92: 173-176.