Journal of Medicinal Plants Research Vol. 5(13), pp. 2599-2607, 4 July, 2011
Available online at http://www.academicjournals.org/JMPR
ISSN 1996-0875 ©2011 Academic Journals

*Review*

# *Hippophae rhamnoides* Linn. for treatment of diabetes mellitus: A review

**Bin Wang, Lan Lin*, Qing Ni and Cheng lian Su**

Endocrinology Department, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China.

Accepted 10 March, 2011

***Hippophae rhamnoides* Linn., commonly known as sea buckthorn (family: Elaeagnaceae), grows wild in Asia and Europe. As one kind of Chinese traditional medicine, *H. rhamnoides* Linn. berry was effective in treating wounds, inflammation, mucous-membrane-related disorders and diseases such as cough, sputum, cancer and bacterial problem. In diabetes, *H. rhamnoides* Linn. affected not only the lowering of the blood sugar including fasting blood glucose and 2 h postprandial blood glucose, but also in treating the complications. *H. rhamnoides* Linn. had been shown to be effective in cell cultures, animal studies, and clinical practice. Although, *H. rhamnoides* Linn. had been shown to have positive effects in relieving symptoms, such as fatigue, dry mouth and dry eye in non-diabetic disease, whether it has the therapeutic effect on diabetes symptoms was still unclear. Studies have to be conducted to test and verify the effect of *H. rhamnoides* Linn. on symptoms in diabetes patients. On the whole, *H. rhamnoides* Linn. is a candidate for complementary diabetes therapy.**

**Key words:** *Hippophae rhamnoides* Linn., diabetes mellitus, blood glucose, complications, symptoms.

## INTRODUCTION

Diabetes mellitus is a metabolic disorder in the endocrine system. The disease is found in all parts of the world and is rapidly increasing in most parts of the world. People suffering from diabetes are not able to produce or properly use insulin in the body, so they have a high content of blood glucose (Li et al., 2004).

The traditional Chinese medicine has demonstrated a good practice and shows a bright future in the therapy of diabetes and its complications because of distinctive traditional medical theory and compositions. In the traditional Chinese medical system, according to its clinical manifestations, diabetes mellitus is categorized as 'Xiao ke zheng' or 'Xiao dan zheng', both of which mean diabetes. *Hippophae rhamnoides* Linn., commonly known as sea buckthorn (family: Elaeagnaceae), grows wild in Asia and Europe. In China, this plant is distributed widely throughout northern and western regions, and is known as '*Sha ji*' by local residents. The ancient Chinese started to use *H. rhamnoides* Linn. more than one thousand years ago. Hundreds of Chinese traditional recipes have utilized the nutritional and medicinal properties of the berry (Zhang W et al., 2010). As one kind of Chinese traditional medicine, *H. rhamnoides* Linn. berry is effective in treating wounds (Gupta et al., 2006), inflammation (Larmo et al., 2008), mucous-membrane-related disorders (Erkkola and Yang, 2003) and diseases such as cough (Lu et al., 2008), bacterial problem(Wu and Zhou, 2004), gastric ulcer (Xing et al., 2002), atopic dermatitis (Yang et al., 1999), liver fibrosis (Gao et al., 2003) and cancer (Grey et al., 2010).

*H. rhamnoides* Linn. contains flavonoids such as isorhamnetin, isorham-netin-3-O-β-D-glucoside, rutin, astragalin, quercetin, myricetin and kaempferol, fatty acids, glycerophospholipids, phytosterols, zexaanthin esters and vitamin C, mineral elements, monosaccharides sugars, organic acids, free amino acids, and vitamin E. The seed contains oil, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, zeaxanthin, sitosterol, vitamin E, vitamin K, carotenoids etc. (Tiitinen et al., 2005; Zeb, 2004; Zeb and Malook, 2009).

*Corresponding author. E-mail: linlgam@163.com Tel: 86-10-88001396.

## EFFECT OF *HIPPOPHAE RHAMNOIDES* LINN. ON HYPERGLYCEMIA

There have been many reports that *Hippophae rhamnoides* Linn. can lower blood sugar in both animals as well as human studies. Oxidative stress plays an important role in the etiology of diabetes and its complications. New methods of treatment for prevention and control of this disease is focus on stopping the oxidative stress.

### Type 1 diabetes mellitus

### Animal studies

Streptozotocins damage the pancreatic islet β-cell and are widely used for experimental diabetes, which closely resembles Type 1 diabetes mellitus (Agarwal, 1980).

Flavonoids from seed of *H. rhamnoides* Linn. could reduce the levels of serum glucose, fructosamine and triglyceride significantly, enhance the ability of antioxidation in streptozotocin STZ-induced diabetic rats (Cao et al., 2005).

### Human studies

Clinical studies have reported that thirty Type 1 diabetic children were treated with *H. rhamnoides* Linn. concentrate for two months, the erythrocyte superoxide dismutase activity and C peptide concentration was significantly higher, and the levels of glycated hemoglobin were significantly lower. The results suggest that *Hippophae rhamnoides Linn*. supplement had a beneficial effect in the treatment of Type 1 diabetic children by oxidative stress pathway (Nemes-Nagy et al., 2008).

### Type 2 diabetes mellitus

### Animal studies

A combination of high-fat diet and low dose of STZ treatment can be effectively used to generate a rat model that mimic the natural history and metabolic characteristics of the common Type 2 diabetes in humans. It is most suited for studying the pathophysiology of Type 2 diabetes and is also useful in evaluating the therapeutic compounds for the treatment of Type 2 diabetes (Srinivasan et al., 2005).

In animal studies, administration of aqueous extract of *H. rhamnoides* Linn. seed residues for 4 weeks significantly lowered the serum glucose, triglyceride and nitric oxide levels and increased markedly serum superoxide dismutase activity and glutathione level in STZ-treated and high fat-diet-fed rats (Zhang et al., 2010).

### Human studies

Postprandial hyperglycemia is the first metabolic abnormality occurring in Type 2 diabetes, and plays an important role in the development of complications associated with the disease, such as micro- and macro-vascular diseases.

Postprandial hyperglycemia control is suggested to play an important role in the treatment of diabetes and prevention of cardiovascular complications (Li et al., 2004).

In human studies, *H. rhamnoides Linn*. had the same effect. Dried and crushed whole *H. rhamnoides* Linn. berries and supercritical fluid-carbon dioxide-extracted oil-free berries suppressed the postprandial peak insulin response and stabilized postprandial hyperglycemia and subsequent hypoglycemia in healthy normal-weight male volunteers after a high-glucose meal (Lehtonen et al., 2010).

## MULTIPLE MECHANISMS BEHIND THE EFFECTS OF LOWERING HYPERGLYCEMIA

Diabetes mellitus is a progressive disease characterized by both insulin resistance and β cell failure, resulting in a decline in insulin secretion and increased blood glucose levels. Studies have shown that *H. rhamnoides* Linn. attenuate hyperglycemia in four ways, the first through enhancing pancreatic β-cell insulin secretion, the second through reducing insulin resistance, the third by increasing the content of liver glycogen and the fourth inhibition the glyconeogenesis.

### Increase insulin secretion

The nature of pancreatic β-cell glucose-sensing is based on two well-defined but not exclusive pathways that couple biochemical and electrical events to insulin release. The first pathway involves the inhibition of $K^+$ efflux through $K_{ATP}$ channels, which is modulated by glucose metabolism and leads to cell membrane depolarization. The second involves a rise in intracellular $Ca^{2+}$ concentration, as a consequence of membrane depolarization and $Ca^{2+}$ influx through L-type $Ca^{2+}$ Channels (Bordin S et al., 1997). *H. rhamnoides* Linn. stimulated insulin release from the β cells through L-type $Ca^{2+}$ channel-mediated pathway in rat. *H. rhamnoides* Linn. also improved antioxidant defense through an increase in superoxide dismutase (SOD) activity which neutralized the reactive oxygen species produced by hyperglycemia (Joantă et al., 2009).

### Increase insulin sensitivity

In the STZ and high-fat diet-induced Type 2 diabetic rats, aqueous extract of *H. rhamnoides* Linn. seed residues

orally administered once a day for 6 weeks could significantly decrease serum glucose and increase insulin sensitivity index by lowering the body weight, total cholesterol and low-density lipoprotein cholesterol levels (Zhang et al., 2010). Total flavones extracted from seed residues of *H. rhamnoides L.* improved insulin sensitivity by suppressing the elevated hyperinsulinemia and dyslipidemia in sucrose-fed rats (Pang et al., 2008).

**Increase liver glycogen content**

Flavonoids from *H. rhamnoides Linn.* significantly elevated insulin and glycogen levels and SOD, GSH-PX and CAT activities, and enhanced antioxidant function and diet level in diabetic mice (Wang et al., 2010).

**Decrease glyconeogenesis**

150 mg/kg flavonoids from the seed residue and fruit residue of *H. rhamnoides Linn.* obviously inhibited the glyconeogenesis in the healthy male mice. Flavonoids from the seed residue and fruit residue of *H. rhamnoides Linn.* decreased the levels of blood glucose and lipid in normal mice, and the effect on glycometabolism may be related to the control of glyconeogenesis (Cao et al., 2003).

## TREAT COMPLICATIONS

Diabetes is a major cause of mortality and morbidity because of its various complications. These complications include various disorders such as hypertensive, lipid metabolism disorders, stroke, coronary heart disease and peripheral vascular disease.

**Hypertensive**

Total flavones extracted from seed residues of *H. rhamnoides Linn.* exerted its antihypertensive effects by improving insulin sensitivity and blocking Angiotensin Ⅱ signal pathway as effective as Angiotensin Ⅱ receptor2008). Total flavonoids of *Hippophae rhamnoides Linn.* could decrease the levels of $[Ca^{2+}]$ (i) in vascular smooth muscle cells of spontaneously hypertensive rats and Wistar-Kyoto rats by blocking both voltage-dependent calcium channels and receptor- operated calcium channels in physiological or pathological state, which may be one of the important mechanisms of their hypotensive and protective effects of anti- hypertensive (Zhu et al., 2005).

**Atherosclerosis**

*H. rhamnoides* Linn. seed oil is a rich source of unsaturated fatty acids, phytosterols, carotenoids and flavonoids, which are known to have significant anti-atherogenic and cardioprotective activity. In cholesterol-fed animals, the blood total cholesterol, triglyceride, low-density lipoprotein-cholesterol and atherosclerosis index were significantly increased and showed a decline following seed oil administration. *H. rhamnoides Linn.* seed oil also increased markedly and restored vasorelaxant activity induced by the acetylcholine (Basu et al., 2007). The flavonoids from *H. rhamnoides Linn.* pretreatment could remarkably prevent both endothelial cell line EA.hy926 death and secretion disorders induced by oxidized low-density lipoprotein in a concentration-dependent manner.Besides, the flavonoids from *H. rhamnoides Linn.* pretreatment could prevent superoxide production and suppress the superoxide dismutase activity triggered by oxidized low-density lipoprotein. Moreover, flavonoids from *H. rhamnoides Linn.* pretreatment partly increased the endothelial nitric oxide synthase expression and decreased lectin-like oxidized Low-density lipoprotein receptor-1 expression (Bao and Lou., 2006). The flavonoids from *H. rhamnoides Linn.* also prevented *in-vivo* thrombogenesis (Cheng et al., 2003; Johansson et al., 2000; Olziikhutag, 1968).

Twenty healthy male volunteers were given either a placebo or *H. rhamnoides Linn.* juice for 8 weeks. A 20% increase in plasma HDL-C concentration was observed. *H. rhamnoides Linn.* juice supplementation also resulted in a moderate decrease in the susceptibility of LDL to oxidation (Eccleston et al., 2002).

In total, 110 female volunteers were recruited, and they followed different berry diets (*H. rhamnoides Linn.*, *H. rhamnoides Linn.* phenolic extract and *H. rhamnoides Linn.* oil) in a randomized order for 33 to 35 days. Vascular cell adhesion molecule decreased after *H. rhamnoides Linn.* oil periods, and in intercellular adhesion molecule after *H. rhamnoides Linn.* phenolic extract diet (Lehtonen et al., 2011).

**Cerebral infarction**

Seed oil of *H. rhamnoides Linn.* 0.7 and 0.35 $g \cdot kg^{-1}$ could markedly reduce infarction volume after occlusion of middle cerebral artery in rats and also could ameliorate the behavior obstacles of rats (Cheng et al., 2003).

Hypoxic stress significantly enhanced the oxidative stress markers such as free radicals and malondialdehyde and it accompanied with decreased levels of antioxidants such as glutathione, glutathione peroxidase and superoxide dismutase. Pretreatment of animals with *H. rhamnoides Linn.* seed oil significantly lowered the levels of free radicals and malondialdehyde. The *H. rhamnoides Linn.* pretreatment also resulted in the significantly improved hypoxic tolerance as evidenced by increased hypoxic gasping time and survival time and decreased plasma catecholamine levels(Purushothaman et al., 2008).

In C-6 glioma cells hypoxia model, the alcoholic leaf extract of *H. rhamnoides* Linn. had the same effect. Exposure of cells to hypoxia for 12 h resulted in a significant increase in cytotoxicity and decrease in mitochondrial transmembrane potential, increase in nitric oxide and reactive oxygen species production and increase in DNA damage during hypoxia. Pretreatment of cells with alcoholic leaf extract of *H. rhamnoides* Linn. at 200 mg/ml significantly inhibited cytotoxicity, ROS production, maintained antioxidant levels, restored the mitochondrial integrity and prevented the DNA damage induced by hypoxia (Narayanan et al., 2005).

### Heart disease

The total flavones of *H. rhamnoides Linn*. could prevent the myocardium from ischemia via decreasing protein expression of *Bax*, increasing *Bcl-2* expression and inhibiting cardiomyocyte apoptosis (Liu et al., 2008; Zhao et al.,2007).The total flavones of *H. rhamnoides Linn*. also could reduce serum and heart advanced glycation end products content (Zhao et al., 2007).

*H. rhamnoides Linn*. could decrease heart rate, lower the expression of alkaline phosphatase in the arteriolar capillary portions of microvessels, and increase the total capillary density in diabetic heart disease model (Koyama et al., 2009).

### Diabetic wound

A poly-herbal formulation prepared by combining the aqueous lyophilized leaf extracts of *H. rhamnoides Linn.*, *Aloe vera Linn.* and the ethanol rhizome extract of *Curcuma longa Linn* treatment increased hydroxyproline and hexosamine content in the STZ-induced diabetic rats wounds. A faster wound contraction was also observed in formulation-treated normal and diabetic rats. The formulation also promoted angiogenesis as evidenced by an *in vitro* chick chorioallantoic membrane model and *in vivo* up-regulated vascular endothelial growth factor expression (Gupta et al., 2008).

## RELIEVE SYMPTOMS

### Fatigue

Among people with diabetes, fatigue is a pervasive and distressing complaint. Although fatigue also occurs in other medical disorders, the importance of fatigue is a great problem in individuals with diabetes. Fatigue in diabetes may be associated with hypo- or hyperglycemia or wide swings between the two. Medicine is needed to be found in order to help people with diabetes to relieve this symptom (Fritschi and Quinn, 2010). There is no effective western medicine to treat the problem, while Chinese medicine has an advantage in relieving symptoms. In the weight carrying swimming mice model, the compound beverage preparation of *H. rhamnoides* Linn. and *Lycium chinense* Mill. remarkably reduced the level of blood lactic acid and the level of serum urea nitrogen, markedly increased the liver glycogen content and swimming duration (Liu et al., 2009).

### Dry mouth

Diabetes mellitus also predisposes to dry mouth. This was explained by hyperglycemia, low stimulated salivary flow rate, or the occurrence of yeast infections. In the Sjögren's syndrome patients, orally ingested *H. rhamnoides Linn.* oil (5 g oil/day) severely reduced complained of subjective symptoms of oral discomfort. In patients who had severely reduced salivary flow and subjective discomfort, *H. rhamnoides Linn.* oil relieved subjective sensations of dry mouth (Le Bell et al., 2001).

### Dry eye

Diabetic patients often complain of dry eye symptoms and have decreased Schirmer test readings. Moreover, their composition of tear proteins is different from that of healthy subjects. In long-lasting diabetes, damage to the microvasculature of the lacrimal gland together with autonomic neuropathy might impair lacrimation (Kaiserman et al., 2005). In the double-blind, randomized, parallel trial, 20- to 75-year-old women and men experiencing dry eye symptoms consumed 2 g of *H. rhamnoides Linn.*oil for 3 months from fall to winter. The maximum intensities of redness and burning tended to be lower in the *H. rhamnoides Linn.* oil group. *H. rhamnoides Linn.* oil could attenuate the increase in tear film osmolarity and positively affected the dry eye symptoms (Larmo et al., 2010).

### Side effects

Goel et al. (2002) investigated the acute toxicity of alcoholic *H. rhamnoides Linn.* berry extract RH-3, which was administered intraperitonially to mice. The single doses of up to 40 mg/kg body weight were tolerated.

According to Tulsawani (2010), the “no observed adverse effect level” of water extract of *Hippophae rhamnoides Linn.* berry in rats administered by gavage for 90 d is 100 mg/kg body weight/ day. No mortality or changes in the general behavior of the animals (15 mice in four groups, administered 0 to 500 mg extract/kg/day) were observed, even at the highest doses used. *H. rhamnoides Linn.* extract in any of the doses did not induce significant changes to the mean body weight, to

the organ/body weight ratio, or to the large variety of histological, hematological and biochemical parameters monitored in the rats as compared to the control group.

Upadhyay et al. (2009) investigated the toxicity of the oil. The rats were given single doses of 2.5 to 10 ml *H. rhamnoides Linn.* seed oil/kg body weight and symptoms of toxicity (mortality, signs of severe toxic symptoms) were monitored for 14 days. No signs of toxicity were observed at any of the doses tested, and the results of the biochemical and hematological analyses did not significantly differ between the treatment and control groups.

Any undesired effects due to *H. rhamnoides Linn.* interventions in clinical studies have been rare (Petra, 2011).

## META-ANALYSES

### Materials and methods

### Literature search and inclusion criteria

We scanned electronic bibliographic databases including Medline (Webspir 1966 to 2008), EMBASE (1984 to 2008), China Biological Medicine Database (CBM-disc 1978 to 2008), China National Knowledge Infrastructure Database (CNKI 1994 to 2008) using combined search terms such as "*H. rhamnoides Linn.*" and "diabetes". Searching by hand for published data through the reference lists of identified articles was also performed.

### Data extraction and methodological quality appraisal

From the studies reviewed, the following data were extracted: animal species, number of animals in treatment and control groups, method of allocation, method of model establishment, the dosage, route and duration of drug administered, result of treatment, and the method used to assess the efficacy of *H. rhamnoides Linn* and its components.

The quality of the studies reviewed was assessed using the following criteria: randomization of the treatment allocation, blinded drug administration, blinded outcome assessment and outcome measurements including both the diabetic conditions (blood glucose level, etc.) and complications (triglyceride, cholesterol, etc.).

### Data analysis

For dichotomous data, the Peto odds ratio (ORs) was calculated. Estimated effect of continuous data was calculated by standardized mean difference (SMD) and 95% confidence interval (CI). For both continuous and dichotomous data, meta-analysis was developed using the statistical software provided by the Cochrane Collaboration (Rev Man 5.0). Heterogeneity between studies was quantified using the $I2 = [(Q-df)/Q]\times100\%$ test (Higgins et al., 2003), where Q is the chi-squared statistic and df is its degrees of freedom .

## Results

### Description of studies

Of the 32 articles identified, 7 articles, including 7 animal studies, were reviewed, with 2 written in English and the rest in Chinese. The included studies are summarized in Table 1. In total, 43 Sprague–Dawley (SD) rats, 20 Wistar rats and 9 NK rats were treated with *H. rhamnoides Linn.*, after the induction of diabetes, while 42 SD rats, 20 Wistar rats and 9 NK rats were used as controls.

### Data analysis

### Fasting blood glucose (FBG)

FBG was measured in 7 studies included in our review. As shown in Figure 1, the SMD was –2.25 (95% CI: –2.40, –2.10, $P < 0.001$), suggesting significant lower FBG levels in the *H. rhamnoides Linn.* treatment group compared to control group.

### Cholesterol

Cholesterol was measured in 4 studies included in our review. As shown in Figure 2, the SMD was –0.51 (95% CI: –0.60,–0.42, $P < 0.001$), suggesting significant lower cholesterol levels in the *H. rhamnoides Linn.* Treatment group compared to model control group.

### Triglyceride

Triglyceride was measured in 4 studies included in our review. As shown in Figure 3, the SMD was –0.19 (95% CI: –0.30, –0.07, $P < 0.01$), suggesting significant lower triglyceride levels in the *H. rhamnoides Linn.* treatment group compared to model control group.

## CONCLUSION AND PROSPECT

It is concluded that *H. rhamnoides* Linn. affects not only the lowering of the blood sugar, including fasting blood glucose and 2 h postprandial blood glucose, but also relieving the symptoms and complications. *H. rhamnoides* Linn. has been shown to be effective in cell cultures, animal studies, and clinical practice.

**Table 1.** Summary of included studies.

| Study ID | Animal Model | Intervention | Outcome | Reference |
|---|---|---|---|---|
| Ai (2008) | Male NK rats. Model control (n = 9); HRL group (n = 9); Model induced with intraperitoneal injection of Alloxan (180 mg/kg); Normal (n = 9). | HRL treatment group: fed with 50 g/kg/d of HRL berries once daily at the same time points for 12 days. Model control group: fed with distilled water at 1ml/kg/d. | 1.Blood glucose 2.Triglyceride 3.Cholesterol | Aimulaguli and Zhang (2008) |
| Cao (2005) | Male SD rats. Model control (n = 10); HRL group (n = 11); Model induced with intraperitoneal injection of STZ (55 mg/kg); Normal (n = 10). | HRL treatment group: fed with 150 mg/kg/d of flavonoids from HRL seed once daily at the same time points for 4 weeks. Model control group: fed with distilled water at 1ml/kg/d. | 1.Blood glucose 2.Triglyceride 3.Cholesterol 4.Glycogen | Cao et al. (2005) |
| Pei (2008) | Male Wistar rats. Model control (n = 10); HRL group (n = 10); Model induced with intraperitoneal injection of STZ (40 mg/kg); Normal (n = 10). | HRL treatment group: fed with 20 mg/kg/d of alcohol extract of HRL berries once daily at the same time points for 4 weeks. Model control group: fed with distilled water at 1ml/kg/d. | 1.Blood glucose 2.Triglyceride 3.Cholesterol | Pei and Cui (2008) |
| Sun (2010) | Male Wistar rats. Model control (n = 8); HRL group (n = 10); Model induced with intraperitoneal injection of STZ (60 mg/kg), Normal (n = 10). | HRL treatment group: fed with 20 mg/kg/d of flavonoids of HRL once daily at the same time points for 14 weeks. Model control group: fed with distilled water at 1ml/kg/d. | Blood glucose | Sun and Zhao (2010) |
| Zhang (2010) | 48 male SD rats. Model control (n = 12); HRL group (n = 12); Model induced with intraperitoneal injection of STZ (45 mg/kg); Normal (n = 12). | HRL treatment group: fed with 400 mg/kg/d of HRL seed residues once daily at the same time points for 4 weeks. Model control group: fed with distilled water at 1ml/kg/d. | 1.Blood glucose 2.Triglyceride 3.Insulin | Zhang et al. (2010) |
| Zhao (2007) | Male SD rats. Model control (n = 10); HRL group (n = 10); Model induced with intraperitoneal injection of STZ (60 mg/kg) Normal (n = 10). | HRL treatment group: fed with 20 mg/kg/d of flavonoids of HRL once daily at the same time points for 12 weeks. Model control group: fed with distilled water at 1ml/kg/d. | Blood glucose | Zhao et al. (2007) |
| Zhou (2007) | Male SD rats. Model control (n = 10); HRL group (n = 10); Model induced with intraperitoneal injection of Alloxan (70 mg/kg); Normal (n = 10). | HRL treatment group: fed with 3600 mg/kg/d HRL once daily at the same time points for 7 days. Model control group: fed with distilled water at 1ml/kg/d. | Blood glucose | Zhou and Zhang (2007) |

Notes: HRL: *H. rhamnoides* Linn.

*H. rhamnoides* Linn. and its extractions exhibit anti-hyperglycemic activities by increasing insulin production and content of liver glycogen, reducing insulin resistance and glyconeogenesis. *H. rhamnoides* Linn. stimulates insulin release from the β cells through L-type $Ca^{2+}$ channel-mediated pathway and decrease oxidative stress. *H. rhamnoides* Linn. has been shown to be anti-hypertensive, anti-atherosclerosis, it could be

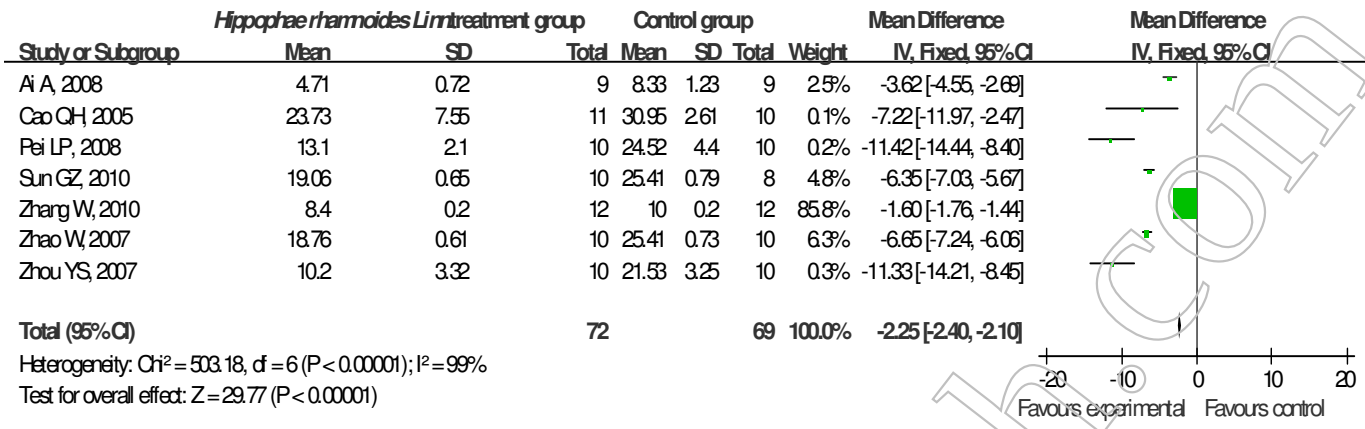


**Figure 1.** Forest plot comparing FBG level in the *Hippophae rhamnoides* Linn. treatment group compared to the model control group.

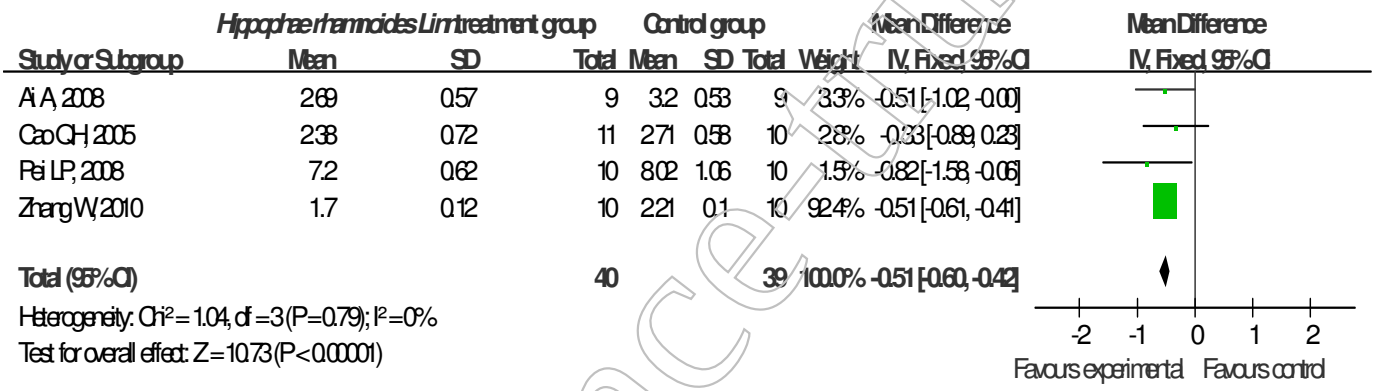


**Figure 2.** Forest plot comparing cholesterol level in the *Hippophae rhamnoides* Linn. treatment group compared to the model control group.

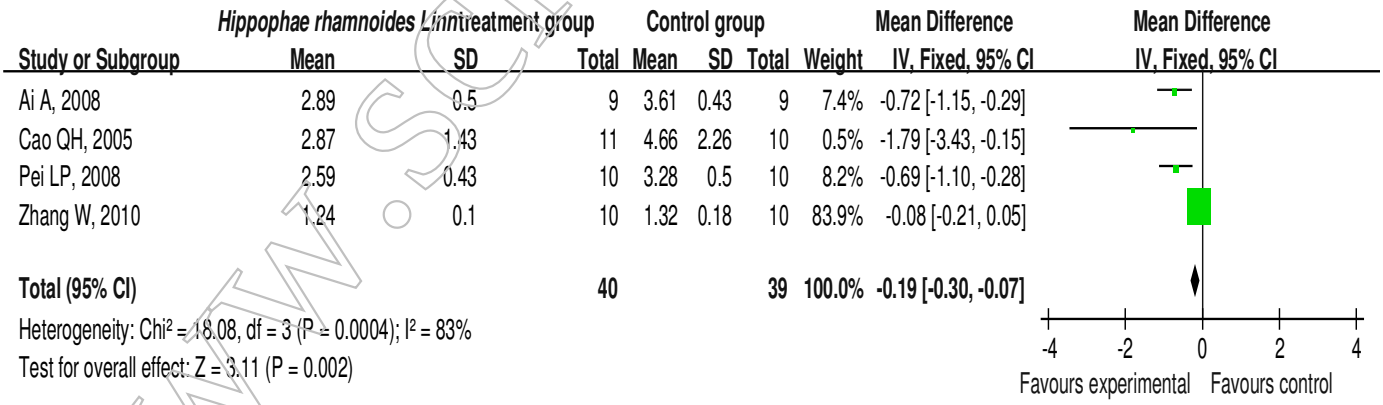


**Figure 3.** Forest plot comparing triglyceride level in the *Hippophae rhamnoides* Linn. treatment group compared to the model control group.

used in treatment of diabetic complications by regulation of lipid metabolism disorder, inhibition cardiomyocyte apoptosis and up-regulation vascular endothelial growth factor expression etc. Although *H. rhamnoides* Linn. has been shown to have positive effects in improving symptoms in non-diabetic disease, whether or not it has

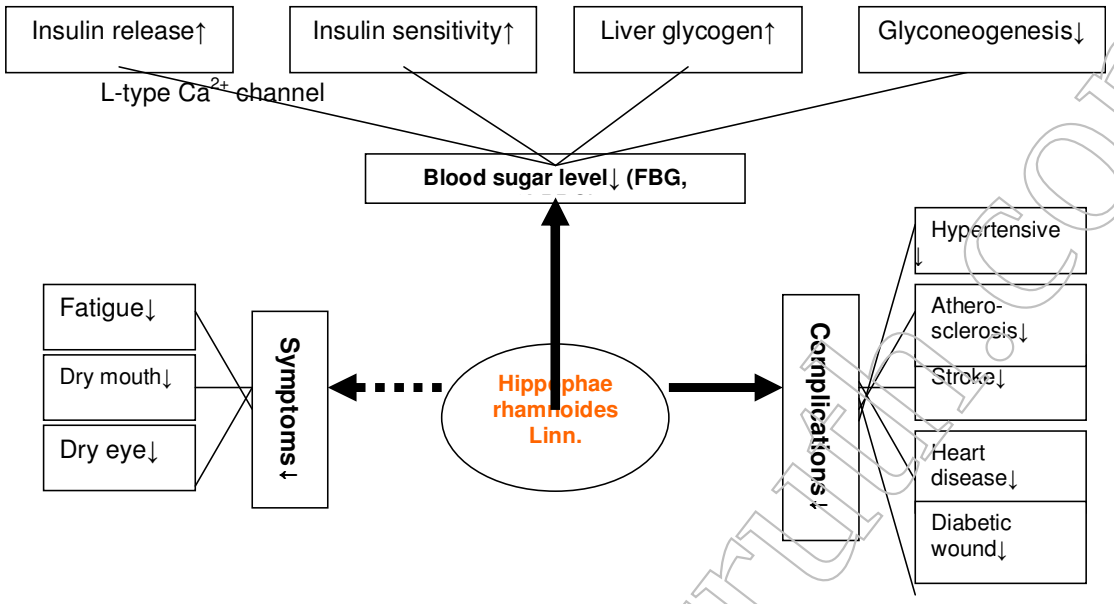


**Figure 4.** The effects and possible mechanisms of *H. rhamnoides* Linn. in treatment of diabetes mellitus. FBG: Fasting blood glucose, 2hPBG: 2-hour postprandial blood glucose.

the therapeutic effect on diabetes symptoms is still unclear (Figure 4). Studies have to be taken to test and verify the effect of *H. rhamnoides* Linn. on diabetes symptoms through animal studies and clinical practice.

We will understand the full extent of its potential until the mechanisms behind *H. rhamnoides* Linn.'s effects have been fully discovered. *H. rhamnoides* Linn. are candidate for complementary diabetes therapy.

## ACKNOWLEDGEMENTS

This work was sponsored by: "Eleventh Five-Year" National Science and Technology Support Project (2006BAI04A04-2-2), National Specific Purpose of Major New Drug "Great platform of research and development of new integrated traditional Chinese medicine " (2009ZX09301-005).

### REFERENCES

Agarwal MK (1980). Streptozotocin: mechanisms of action. Febs Lett., 120: 1-3.

Aimulaguli A, Zhang YC (2008). Effect on mice blood sugar and blood grease with Hippophae. J. Xinjiang Norm. Univ. (Nat. Sci. Ed.), 27(4): 39-42.

Bao M, Lou Y (2006). Flavonoids from sea buckthorn protect endothelial cells (EA.hy926) from oxidized low-density lipoprotein induced injuries via regulation of LOX-1 and eNOS expression. J. Cardiovasc. Pharmacol., 48(1): 834-841.

Basu M, Prasad R, Jayamurthy P, Pal K, Arumughan C, Sawhney RC (2007). Anti-atherogenic effects of sea buckthorn (*Hippophaea rhamnoides*) seed oil. Phytomed., 14(11): 770-777.

Bordin S, Carneiro EM, Bosqueiro JR, Boschero AC (1997). Tetracaine stimulates extracellular $Ca2^{+}$-independent insulin release. Eur. J. Pharmacol., 327(2-3): 257-262.

Cao Q, Qu W, Deng Y, Zhang Z, Niu W, Pan Y (2003). Effect of flavonoids from the seed and fruit residue of *Hippophae rhamnoides L.* on glycometabolism in mice. Zhong. Yao. Cai., 26(10): 735-737.

Cao Q, Qu WJ, Niu W, Deng YX, Wang YW, Xie JJ (2005). The antihyperglycemic effect of flavonoids from *Hippophae Rhamnoides L.* on diabetic rats induced by streptozocin. Acta. Nutr. Sin., 27(2): 151-154.

Cheng J, Kondo K, Suzuki Y, Ikeda Y, Meng X, Umemura K (2003). Inhibitory effects of total flavones of *Hippophae Rhamnoides L* on thrombosis in mouse femoral artery and *m* platelet aggregation. Life Sci., 72(20): 2263-2271.

Cheng TJ, Wang YB, Gao LP, Sun YF, Zhang J (2003). The protection of seed oil of *Hippophae rharmnoides* on ischemic cerebral infarction in rats. Zhongguo. Zhong. Yao. Za. Zhi. 28(6): 548-550.

Eccleston C, Baoru Y, Tahvonen R, Kallio H, Rimbach GH, Minihane AM (2002). Effects of an antioxidant-rich juice (sea buckthorn) on risk factors for coronary heart disease in humans. J. Nutr. Biochem., 13(6): 346-354.

Erkkola R, Yang B (2003). Sea buckthorn oils: towards healthy mucous membranes. Agro Food. Ind. hi-tech., 3: 53-57.

Fritschi C, Quinn L (2010). Fatigue in patients with diabetes: a review. J. Psychosom. Res., 69(1):33-41.

Gao ZL, Gu XH, Cheng FT, Jiang FH (2003). Effect of sea buckthorn on liver fibrosis: a clinical study. World. J. Gastroenterol., 9(7): 1615-1617.

Goel HC, Prasad J, Singh S, Sagar RK, Kumar IP, Sinha AK (2002). Radioprotection by a herbal preparation of Hippophae rhamnoides, RH-3, against whole body lethal irradiation in mice. Phytomed., 9: 15-25.

Grey C, Widen C, Adlercreutz P, Rumpunen K, Duan RD (2010). Antiproliferative effects of sea buckthorn (*Hippophae rhamnoides L.*) extracts on human colon and liver cancer cell lines. Food. Chem., 120(4): 1004-1010.

Gupta A, Kumar R, Pal K, Singh V, Banerjee PK, Sawhney RC (2006). Influence of sea buckthorn (*Hippophae rhamnoides* L.) flavone on

dermal wound healing in rats. Mol. Cell. Biochem., 290(1-2): 193-198.
Gupta A, Upadhyay NK, Sawhney RC, Kumar R (2008). A poly-herbal formulation accelerates normal and impaired diabetic wound healing. Wound. Repair. Regen., 16(6): 784-790.
Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003). Measuring inconsistency in meta-analyses. BMJ, 327(7414): 557-560.
Joantă AE, Şarlea SV, Login C, Socaciu C, Decea N, Moldovan R, Damian A (2009). Hippophae Rhamnoides interferes with insulin release via L-type $Ca^{2+}$ channel-mediated pathway in rat islet β cells. Bull.UASMV. Vet. Med., 1: 207-213.
Johansson AK, Korte H, Yang B, Stanley JC, Kallio HP (2000). Sea buckthorn berry oil inhibits platelet aggregation. J. Nutr. Biochem., 11(10): 491-495.
Kaiserman I, Kaiserman N, Nakar S, Vinker S (2005). Dry eye in diabetic patients. Am. J. Ophthalmol., 139(3): 498-503.
Koyama T, Taka A, Togashi H (2009). Effects of a herbal medicine, *Hippophae rhamnoides*, on cardiovascular functions and coronary microvessels in the spontaneously hypertensive stroke-prone rat. Clin. Hemorheol. Microcirc., 41(1): 17-26.
Larmo P, Alin J, Salminen E, Kallio H, Tahvonen R (2008). Effects of sea buckthorn berries on infections and inflammation: a double-blind, randomized, placebo-controlled trial. Eur. J. Clin. Nutr., 62(9): 1123-1130.
Larmo PS, Järvinen RL, Setälä NL, Yang B, Viitanen MH, Engblom JR, Tahvonen RL, Kallio HP (2010). Oral sea buckthorn oil attenuates tear film osmolarity and symptoms in individuals with dry eye. J. Nutr., 140(8): 1462-1468.
Le bell AM, Soderling E, Rantanen I, Yang B, Kallio H (2001). Effects of sea buck thorn oil on the oral mucosa of Sjögren's syndrome patients: a pilot study. Poster at The eightieth General Session and Exhibition of International Association for Dental Research (IADR). San Diego, USA.
Lehtonen HM, Järvinen R, Linderborg K, Viitanen M, Venojärvi M, Alanko H, Kallio H (2010). Postprandial hyperglycemia and insulin response are affected by *Hippophae rhamnoides* Linn. (Hippophaë rhamnoides ssp. turkestanica) berry and its ethanol-soluble metabolites. Eur. J. Clin. Nutr., 64(12): 1465-1471.
Lehtonen HM, Suomela JP, Tahvonen R, Yang B, Venojärvi M, Viikari J, Kallio H (2011). Different berries and berry fractions have various but slightly positive effects on the associated variables of metabolic diseases on overweight and obese women. Eur. J. Clin. Nutr., 65(3): 394-401.
Li WL, Zheng HC, Bukuru J, De Kimpe N (2004). Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. J. Ethnopharmacol., 92: 1–21.
Li Y, Peng G, Li Q, Wen S, Huang TH, Roufogalis BD, Yamahara J (2004). *Salacia oblonga* improves cardiac fibrosis and inhibits postprandial hyperglycemia in obese zucker rats. Life Sci., 75(14): 1735-1746.
Liu HY, Li MX, Xue YH, An JG (2009). An experimental study on fatigue resistance action of compound beverage preparation of matrimony vine and sea buckthorn on mice. J. Baotou. Med. Coll. (6): 17-19.
Liu ZR, Zhang Q, Yang YM, Guan H, Liu FM (2008). Changes of proteomic spectra of total flavones of *Hippophae rhamnoides* on myocardial protection. Zhong. Guo. Zhong. Yao. Za. Zhi., 33(9): 1060-1063.
Lu CZ, Shan YK, Liu HZ, Yang LH (2008). The development of oral solution from Sea buckthorn and pear juice for cough. Glo. Seabuckthorn. Res. Dev., 4: 1-5.
mice with alloxan induced diabetes. Food. Sci., 31(7): 297-301.
Narayanan S, Ruma D, Gitika B, Sharma SK, Pauline T, Ram MS, Ilavazhagan G, Sawhney RC, Kumar D, Banerjee PK (2005). Antioxidant activities of sea buckthorn (*Hippophae rhamnoides*) during hypoxia induced oxidative stress in glial cells. Mol. Cell. Biochem., 278(1-2): 9-14.
Nemes-Nagy E, Szőcs-Molnár T, Dunca I, Balogh-Sămărghiţan V, Hobai Ş, Morar R, Pusta DL, Crăciun EC (2008). Effect of a dietary supplement containing blueberry and *Hippophae rhamnoides* Linn. concentrate on antioxidant capacity in type 1 diabetic children. Acta. Physiol. Hung., 95(4): 383-393.
Olziikhutag A (1968). Influence of sea-buckthorn oil on the development of experimental atherosclerosis in rabbits. Cor. Vasa., 10(1): 59-67.
Pang X, Zhao J, Zhang W, Zhuang X, Wang J, Xu R, Xu Z, Qu W (2008). Antihypertensive effect of total flavones extracted from seed residues of *Hippophae rhamnoides L.* in sucrose-fed rats. J. Ethnopharmacol., 117(2): 325-331.
Pei LP, Cui J (2008). Study on protective effects of Hippophae rhamnoides L. fruit on type 2 diabetic rat model. J. Centrl. Univ. Nationaliti. (Nat. Sci Ed.)., 17(4): 81-84.
Petra L (2011). The health effects of Sea buckthorn berries and oil. University of Turku.
Purushothaman J, Suryakumar G, Shukla D, Malhotra AS, Kasiganesan H, Kumar R, Sawhney RC, Chami A (2008). Modulatory effects of sea buckthorn (*Hippophae rhamnoides* L.) in hypobaric hypoxia induced cerebral vascular injury. Brain. Res. Bull., 77(5): 246-252.
Srinivasan K, Viswanad B, Asrat L, Kaul CL, Ramarao P (2005). Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening. Pharmacol. Res., 52(4): 313-320.
Sun GZ, Zhao W (2010). The effect of flavonoids of sea buckthorn on myocardial cells in diabetic rats. HeiLongJiang. Med. Pharm., 33(3): 51-52.
Tiitinen KM, Hakala MA, Kallio HP (2005). Quality components of sea buckthorn (*Hippophae rhamnoides*) varieties. J. Agric. Food. Chem., 53(5): 1692-1629.
Tulsawani R (2010). Ninety day repeated gavage admistration of Hippophae rhamnoides extract in rats. Food. Chem. Toxicol., 48(8-9): 2483-2489.
Upadhyay NK, Kumar R, Mandotra SK, Meena RN, Siddiqui MS, Sawhney RC, Gupta A (2009). Safety and healing efficacy of sea buckthorn (Hippophae rhamnoides L.) seed oil on burn wounds in rats. Food Chem. Toxicol., 47:1146-1153.
Wang ZY, Liu Y, Zhou LP (2010). Hypolipidemic and antioxidant effects of flavonoids from *Hippophae rhamnoides L.*pomace in ICR
Wu SQ, Zhou DL (2004). A research of that sea buckthorn rice vinegar restrain the germ function to the Escherichia coli. J. Changchun. Uni., 6: 85-86.
Xing J, Yang B, Dong Y, Wang B, Wang J, Kallio HP (2002). Effects of sea buckthorn (*Hippophaë rhamnoides* L.) seed and pulp oils on experimental models of gastric ulcer in rats. Fitoterapia. 73(7-8): 644-650.
Yang B, Kalimo KO, Mattila LM, Kallio SE, Katajisto JK, Peltola OJ, Kallio HP (1999). Effects of dietary supplementation with sea buckthorn (*Hippophaë rhamnoides*) seed and pulp oils on atopic dermatitis. J. Nutr. Biochem., 10(11): 622-630.
Zeb A (2004). Chemical and nutritional constituents of sea buckthorn juice. Pak. J. Nutr., 3(2): 99-106.
Zeb A, Malook I (2009). Biochemical characterization of sea buckthorn (*Hippophae rhamnoides* L. spp. turkestanica) seed. Afr. J. Biotechnol., 8(8): 1625-1629.
Zhang W, Zhao J, Wang J, Pang X, Zhuang X, Zhu X, Qu W (2010). Hypoglycemic effect of aqueous extract of sea buckthorn (*Hippophae rhamnoides L.*) seed residues in streptozotocin-induced diabetic rats. Phytother. Res., 24(2): 228-232.
Zhang W, Zhao JJ, Zhu XL, Zhuang XY, Pang XF, Wang JS, Qu WJ (2010). Antihyperglycemic effect of aqueous extract of Hippophae Rhamnoides Linn. (*Hippophae Rhamnoides L.*) seed residues in streptozotocin-treated and high fat-diet-fed rats. J. Food. Biochem., 34(4): 856-868.
Zhao W, Sheng YL, Liu YX, Li RX, Sun GZ, Jiang XD, Yuan DX, Wang SQ (2007). Effect of total flavones of *Hippophae rhamnoides L.* on the AGEs in diabetic rat heart. Heilongjiang. Med. Pharm., 30(2): 49.
Zhao W, Sun GZ, Li RX, Huo JM (2007). Effect of total flavones of *Hippophae rhamnoides* L. on the Bax, Bcl-2 protein expression in diabetic rat heart cells. Chin. J. Comp. Med. 2007, 17(8): 62-63.
Zhou YS, Zhang JJ (2007). Hypoglycemic effect of Sea buckthorn extract on alloxan diabetic mice. HIPPOPHAE, 20(3): 25-26.
Zhu F, Huang B, Hu CY, Jiang QY, Lu ZG, Lu M, Wang MH, Gong M, Qiao CP, Chen W, Huang PH (2005). Effects of total flavonoids of *Hippophae rhamnoides L.* on intracellular free calcium in cultured vascular smooth muscle cells of spontaneously hypertensive rats and Wistar-Kyoto rats. Chin. J. Integr. Med., 11(4): 287-292.