Natural Product Sciences
16(4) : 239-244 (2010)

Screening of Protein Tyrosine Phosphatase 1B Inhibitory Activity from Some Vietnamese Medicinal Plants

Duc Manh Hoang[1,†], Trinh Nam Trung[2,4,†], Phan Thi Thu Hien[3], Do Thi Ha[2,5], Hoang Van Luong[4], Myoungsook Lee[1,*], and KiHwan Bae[2,*]

[1]*Research Institute of Obesity Science, and Dept. of Food and Nutrition, Sungshin Women's University, Seoul 136-74, Republic of Korea*
[2]*College of Pharmacy, Chungnam National University, Daejeon 305-764, Korea*
[3]*Traditional Medicinal Departments, Ministry of Health, Ba Dinh, Hanoi, Vietnam*
[4]*Vietnam Military Medical University, Hadong, Hanoi, Vietnam*
[5]*National Institute of Medicinal Materials, 3B Quangtrung, Hoankiem, Hanoi, Vietnam*

Abstract – Protein tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin signaling, has served as a potential drug target for the treatment of type 2 diabetes. The MeOH extracts of twenty-nine medicinal plants, traditionally used in Vietnam as anti-diabetes agents, were investigated for PTP1B inhibitory activity *in vitro*. The results indicated that, most materials showed moderate to strong inhibitory activity with IC_{50} values ranging from 3.4 μg/mL to 35.1 μg/mL; meanwhile, eleven extracts (37.9%) could demonstrate PTP1B activity with IC_{50} values less than 15.5 μg/mL; sixteen extracts (55.2%) could demonstrate PTP1B activity with IC_{50} values ranging from 15.5 μg/mL to 35.1 μg/mL. The study may provide a proof, at least in a part, for the ethno-medical use in diabetes disease of these plants.
Keywords – Vietnamese medicinal plants, Protein tyrosine phosphatase 1B (PTP1B), diabetes

Diabetes mellitus, often simply referred to as diabetes is a condition in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. The characteristic symptoms are excessive urine production (polyuria), excessive thirst and increased fluid intake (polydipsia), and increased food intake (polyphagia). More than 80% of people with type 2 diabetes will live in developing countries (White and Rafique, 2002). Those of underdeveloped countries including Vietnam cannot afford the increasing burden of chronic renal failure and blindness. The large poor populations has lower prevalence rates than the rich, but have higher rates of complications because of later diagnosis, inaction on risk factors, and poor management. In 1990s, about 1 - 1.5% Vietnamese people were affected by diabetes which would increased to 4% by 2001 but at least 70% patients were clearly not excavated and had right treatment (Vietnam National Diabetes Federation Conference, June 2003). Therefore, there is an urgent need to develop necessary therapies for these diseases.

The reversible protein tyrosine phosphorylation by protein tyrosine kinases (PTK) and protein tyrosine phosphatases (PTP) is a key element of the signaling pathways induced by environmental stimuli (Wang *et al.*, 2003; Tonks, 2003).

One of the intracellular PTPase, PTP1B has been implicated in negative regulation of the insulin signaling by dephosphorylating the insulin receptor (IR) as well as its substrate IRS-1 and IRS-2 (Kenner *et al.*, 1996; Seely *et al.*, 1996). The protein levels are increased in insulin-resistant diabetes patients and the deletion of PTP1B in mice has been shown to increase insulin sensitivity (Ahmad *et al.*, 1995; Elchebly *et al.*, 1999; Klaman *et al.*, 2000). Inhibiting PTP1B action using antisense oligonucleotides and small molecule inhibitors represents novel therapeutic approach for the treatment of insulin resistance (Zinker *et al.*, 2002; Xie *et al.*, 2003). It is well established that insulin signaling, in particular activation of insulin receptor and insulin receptor substrates, is impaired in most patients with type 2 diabetes (Johnson *et al.*, 2002). Protein tyrosine phosphatases (PTPs) are

† These authors contributed equally to this work.
*Author for correspondence
Tel: +82-2-920-7211; E-mail: mslee@sungshin.ac.kr
Tel: +82-42-821-5925; E-mail: baekh@cnu.ac.kr

responsible for the dephosphorylation of tyrosine residues, and are considered negative regulators of insulin signaling. Several PTPs such as PTP-α, leukocyte antigen-related tyrosine phosphatase (LAR), and SH2-domain containing phosphotyrosine phosphatase (SHP2) have been implicated in the regulation of insulin signaling, there is substantial evidence supporting protein tyrosine phosphatase 1B (PTP1B) as the critical PTP-controlling insulin signaling pathway (Johnson *et al*., 2002). In addition, in cultured cells, overexpression of PTP1B markedly inhibits insulin effect on its receptor phosphorylation (Kenner *et al*., 1996). A study with PTP1B knockout mice has shown that PTP1B knockout resulted in mice with marked increase in insulin sensitivity and which are resistant to diet induced obesity (Enchebly *et al*., 1999). Based on these various findings, PTP1B is considered as one of promising targets in the treatment of diabetes but also obesity, and several classes of plant-derived secondary metabolites have been described as PTP1B inhibitors (Tonks, 2003).

Natural products are tremendous sources of lead compounds in the search for new medicaments for the treatment of disease. The largest present underexplored source of such materials lies in tropical and subtropical regions of the world. In these areas, a long tradition of ethno-botanical medicine often exists and offers a rich and relatively untapped source for the discovery of new drugs from natural products. Vietnamese, a Southeast Asian tropical country, has a rich plant biodiversity, with over 12,000 plants and no less than 2,500 species have been used in ethno-medicine (Chi, 1997; Loi, 2004). Thus, as part of a permanent screen program searching for Vietnamese medicinal plants and natural products, the aim of this study was to discover whether there was some scientific basis for the reputed efficacy of selected traditional medicinal plants from Vietnam in treatment of anti-diabetes. Selection was based on literature research of traditional medicinal plant usage in Vietnam (Loi, 2004).

Materials and Methods

Plant materials – Vietnamese medicinal plants used in this study were collected in the North of Vietnam in spring, 2010. The botanical samples were identified (Table 1) by Prof. Pham Thanh Ky, Department of Botany, Hanoi University of Pharmacy, Vietnam, where the voucher specimens were deposited. The plants were dried for 7 - 10 days in the shade at environmental temperatures. The dried plants were then ground and transfer to the laboratory for preparation of the plant extracts.

Preparation of samples – The air-dried and powdered parts of different amount of plants were extracted with methanol at room temperature (25 °C) by maceration process for 72 hr. The crude extracts were obtained after evaporation of solvent under reduced pressure at 40 °C. Percentage yields (w/w) were calculated (Table 1). All extracts were stored at –20 °C prior to screening.

Protein Tyrosine Phosphatase 1B inhibitory activity assay – PTP1B (human, recombinant) was purchased from BIOMOL® International LP (USA) and the enzyme activity was measured using *p*-nitrophenyl phosphate (*p*-NPP) as a substrate. To each 96-well (final volume: 200 μL) were added 2 mM *p*-NPP and PTP1B (0.05 - 0.1 μg) in a buffer containing 50 mM citrate (pH 6.0), 0.1 M NaCl, 1 mM EDTA, and 1 mM dithiothreitol (DTT) with or without test compounds. Following incubation at 37 °C for 30 min, the reaction was terminated with 10 M NaOH. The amount of produced *p*-nitro phenol was estimated by measuring the absorbance at 405 nm. The nonenzymatic hydrolysis of 2 mM *p*-NPP was corrected by measuring the increase in absorbance at 405 nm obtained in the absence of PTP1B enzyme.

Statistical analysis – The results were expressed as mean ± SD of three determinations at each concentration for each sample. The inhibitory concentration 50% (IC_{50}) was calculated using Microsoft Excel program. Statistical significance was calculated by one-way analysis of variance (ANOVA), followed by Dunnett's test.

Results and Discussion

The plants are listed in alphabetical order of their scientific name, family name, local name, part used and also therapeutic application (Table 1). In the present study, twenty-nine plants species which belonging to twenty-two families were selected, and total of twenty-nine extracts were investigated based on their ethno-medical use for the treatment of diabetes and related diseases by the natives of Vietnamese folk medicinal system (Loi, 2001). The inhibitory effect of twenty-nine extracts on PTP1B activity is summarized (Table 2). Of the twenty-nine extracts assayed, twenty-seven extracts (93.1%) could demonstrate PTP1B activity with IC_{50} values no higher than 36.0 μg/mL (Table 2). The result revealed that the extract of *Morus sp.* possessed the most potent effect with IC_{50} as 3.4 μg/mL followed by radix *Glycyrrhizae* (IC_{50} = 3.7 μg/mL), *Phyllanthus reliculatus* (IC_{50} = 4.5 μg/mL), *Tetracera scandens* (IC_{50} = 5.2 μg/mL), *Erythrina variegata* (IC_{50} = 7.4 μg/mL), *Dioscorea persimilis* (IC_{50} = 7.5 μg/mL), *Eurya nitida* (IC_{50} = 8.7 μg/mL), *Plantago asiatica*

Table 1. Vietnamese Medicinal Plants used in this study

No	Plant species	Family	Part used	Local name	Yield (%)[a]
01	*Arctium lappa L.*	Asteraceae	Fruit	Nguu bang	2.13
02	*Asparagus cochinchinensis (Lour)*	Liliaceae	Root	Thien mon	2.61
03	*Atractylodes macrocephala*	Asteraceae	Rhizome	Bach truat	1.25
04	*Biophytum sensitivum (Lour.)*	Oxalidaceae	Leaf	La chua me	0.92
05	*Carthamus tinctorius L.*	Asteraceae	Flower	Hong hoa	3.41
06	*Catharanthus roseus*	Apocynaceae	Whole plant	Dua can	5.39
07	*Cinnamomum cassia*	Lauraceae	Bark	Que	4.68
08	*Curcuma longa L.*	Zingiberaceae	Rhizome	Nghe	3.26
09	*Cynara scolymus L.*	Asteraceae	Leaf	Actiso	2.11
10	*Cyrtomium fortunei*	Polypodiaceae	Rhizome	Quan hung	1.75
11	*Dioscorea persimilis*	Dioscoraceae	Rhizome	Hoai son	1.27
12	*Erythrina variegata*	Papilionaceae	Leaf	Vong nem	2.81
13	*Eurya nitida Korth*	Theaceae	Leaf	Che Sum	3.23
14	*Eurylale ferox Salisb*	Nymphaeaceae	Seed	Khiem thuc	1.33
15	*Radix Glycyrrhizae*	Leguminosae	Root	Cam thao	6.12
16	*Gynostemma pentaphyllum*	Cucurbitaceae	Whole plant	Giao Co Lam	1.31
17	*Imperata cylindrica*	Poaceae	Rhizome	Co tranh	1.26
18	*Leonurus heterophyllus Sweet.*	Lamiaceae	Aerial part	Ich mau	2.16
19	*Lycium chinensis Mill*	Solanaceae	Rhizome	Dia cot bi	0.82
20	*Momordica charantia*	Cucurbitaceae	Fruit	Muop dang	1.61
21	*Morus sp.*	Moraceae	Leaf	Dau	3.25
22	*Phyllanthus reticulatus Poir.*	Euphorbiaceae	Aerial part	Phen den	2.61
23	*Plantago asiatica*	Plantaginaceae	Root, stem	Ma de	3.52
24	*Polygonum multiflorum Thunb*	Polygonaceae	Rhizome	Ha thu o do	3.17
25	*Poria cocos Wolf*	Polyporaceae	Aerial part	Phuc linh	1.24
26	*Rehmannia glutinosa Libosch*	Scrophulariaceae	Rhizome	Sinh dia hoang	0.17
27	*Taraxacum officinale*	Asteraceae	Whole plant	Bo cong anh	1.42
28	*Tetracera scandens L.*	Dilleniaceae	Branches	Chac chiu	2.81
29	*Xanthium strumarium L.*	Asteraceae	Fruit	Ke dau ngua	3.51

[a] Percentage extract yield (w/w) was calculated as (dry extract weight/dry starting material weight) × 100.

(IC_{50} = 9.2 μg/mL), *Polygonum multiflorum* (IC_{50} = 10.2 μg/mL), *Carthamus tinctorius* (IC_{50} = 10.5 μg/mL), *Gynostemma pentaphyllum* (IC_{50} = 11.9 μg/mL). Some other plant extracts such as *Atractylodes macrocephala*, *Cinnamomum cassia*, *Curcuma longa*, *Cynara scolymus*, *Momordica charantia*, *Leonurus heterophyllus*, *Poria cocos*, *Taraxacum officinale*, and *Xanthium strumarium* expressed inhibitory activity with IC_{50} values ranging from 13.7 μg/mL to approximately 35.1 μg/mL. In this study, RK-682 (5.0 ± 0.5 μM) and ursolic acid (3.9 ± 0.3 μM) were used as positive control. Two other plants (*Eurylale ferox* and *Lycium chinensis*) were apparently inactive or very weak activity with IC_{50} > 50 μg/mL.

Morus species has been used in traditional medicine for treating diabetes, diuretic, expectorant, and laxative agents (Loi, 2004). Chemical and pharmacological investigations on *Morus sp.* have resulted in the isolation of series of prenylated flavonoids, benzofurans, and other phenolic compounds (Fukai, 1985; Nomura, 1983) which have been found to exhibit cytotoxicity and inhibition of COX-1, COX-2, NO production and HIF1 (Shi, 2001; Sohn, 2004; Dat, 2009) and also several flavonoids were isolated and reported as PTP1B inhibitors (Cui, 2006; Hoang, 2009).

Licorice, the roots and rhizomes of some *Glycyrrhiza* species (Leguminosae) has been used by human being for at least 400 years. Clinical studies of licorice make it one of the most thoroughly studied herbs, which includes antimutagenic activity (Ngo *et al*., 1992; Zani F., 1993), anti-ulcer effect (Takagi K., 1967), protective action for hepatotoxicity (Nose M., 1994) antitumor promoting activity (Nishino H., 1986), antimicrobial effect (Haraguchi H.,

Table 2. PTP1B Inhibitory Activity of Vietnamese Medicinal Plants

Plant	Inhibitory activity (IC_{50} μg/mL) [a]
Arctium lappa	32.4 ± 1.3
Asparagus cochinchinensis	29.6 ± 0.9
Atractylodes macrocephala	19.5 ± 1.2
Biophytum sensitivum	26.7 ± 1.1
Carthamus tinctorius	10.9 ± 0.9
Cinnamomum cassia	16.8 ± 0.7
Curcuma longa	17.8 ± 1.1
Cynara scolymus	13.7 ± 0.7
Cyrtomium fortunei	21.7 ± 0.8
Dioscorea persimilis	7.5 ± 0.7
Erythrina variegata	7.4 ± 0.6
Eurya nitida Korth	8.7 ± 0.8
Eurylale ferox Salisb	> 50
Radix Glycyrrhizae	3.7 ± 0.4
Gynostemma pentaphyllum	11.9 ± 1.2
Imperata cylindrica	27.6 ± 1.1
Leonurus heterophyllus	25.2 ± 0.9
Lycium chinensis	> 50
Momordica charantia	15.6 ± 1.5
Morus sp.	3.4 ± 0.4
Phyllanthus reticulatus	4.5 ± 0.3
Plantago asiatica	9.2 ± 0.5
Polygonum multiflorum	10.2 ± 0.6
Poria cocos	23.3 ± 0.9
Rehmannia glutinosa	35.1 ± 2.1
Taraxacum officinale	25.5 ± 0.8
Tetracera scandens	5.2 ± 0.7
Xanthium strumarium	28.5 ± 1.2
RK-682[b]	5.0 ± 0.5
Ursolic acid[b]	3.9 ± 0.3

[a] IC_{50} values were determined by regression analyses and expressed as mean ± SD of three replicates.
[b] Positive control (Na et al., 2006).

1998), *etc.* Much of the recent research on licorice constituents has revealed the pharmacological importance of phenolic compounds. Many studies on the flavonoid constituents of *Glycyrrhiza* species have been carried out, and more than sixty phenolic compounds have been isolated from the underground parts of *Glycyrrhiza*. Glabridin, the major flavonoid of licorice was investigated on abdominal fat accumulation and blood glucose level in obese diabetic KK-Ay mice (Nakagawa, 2004).

The natural resource of wild *Glycyrrhiza* is about exhaustion. Therefore, this plant is cultivated in a large scale in the Inner Mongolia area, China and other Asia countries.

Some on the other plants presented interesting activities against PTP1B enzyme such as *Carthamus tinctorius*, *Cynara scolymus*, *Cinnamomum cassia*, *Dioscorea persimilis*, *Eurya nitida*, *Gynostemma pentaphyllum*, *Momordica charantia*, *Plantago asiatica*, *Polygonum multiflorum*, *Rehmannia glutinosa*, and *Tetracera scandens*. *Catharanthus roseus* is an important medicinal plant which can against normal and streptozotocin-induced diabetic rat models by blood sugar lowering capacity, and its antidiabetic activity seems to be a result of increase in glucose utilization (Chattopadhyay, 1999; Singh, 2001). The rich of flavonoids and indole alkaloids containing in this plant may have revealed corresponding for these activity (Schroder, 2004). For the plant *C. tinctorius*, the anti-diabetic composition comprises shows a high antihyperglycemic effect and a maltase-inhibitory or reducing effect (Satoru, 2005). These activities could be linked to the presence and structural transformation of lignans, quinochalcone and flavonoid in the petals (Nose, 1992; Meselhy, 1993). *M. charantia* was used in various systems of traditional medicine for diabetes and its complications as nephropathy, cataract, insulin resistance (Grover and Yadav, 2004; Ahmed, 2001; Welihinda, 1986). *G. pentaphyllum* is a traditional agent for treatment of elevated cholesterol (Djang, 2005). Its extract inhibited α-glucosidase activity, and has effectiveness in obese Zucker fatty diabetic rat model (Megalli, 2006). Recent published paper showed that phanoside, a gypenoside isolated from this plant, stimulates insulin secretion from rat pancreatic islets (Hoa, 2007). The radix of *R. glutinosa* is one component of the Seishin-kanro-to which used in patients with diabetes traditional medicine (Miura, 1997). In alloxan-induced diabetic rats, its oligosaccharide showed a significant decrease in blood glucose level, hepatic glucose-6-phosphatase activity with an increase in hepatic glycogen content, raised plasma insulin level and lowered plasma corticosterone level (Zhang, 2004).

In Vietnam, the use of those medicinal plants and herbal therapy has been practiced long before recorded history. However, the potential use of them or other anti-diabetes plants as the source of new drugs is still poorly explored. In most case, only pharmacological screening or preliminary studies have been carried out. It is possible to note that alkaloids, flavonoids, terpenoids, lignans and/or other phytochemical constituents containing in those plant play important role for their biological activities. In this study, some of the selected plants could not manifest the ability effects but some of them presented interesting in vitro activities against PTP1B enzymes. This may suggest that these plant extract might be interacting with the

enzymes in different mechanisms.

This is the first time the inhibitory activity of *C. roseus*, *C. tinctorius*, *M. charantia*, *G. pentaphyllum*, *T. scandens*, *Glycyrrhiza*, *R. glutinosa*, in PTP1B were exhibited. Specially, *G. pentaphyllum* extract reportedly have many effects, such as lowered cholesterol, immunopotentiation, as well as antitumor, antioxidant, and hypoglycemic effects. A large group of substances in this extract is saponins as gypenosides which can be representatives of gypenosides from ginseng (Norberg et al., 2004). Other example may be listed with *T. scandens* which are mainly used for treatment of inflammation; it is possible that this extract may reduce the effect of inflammatory cytokine release during diabetes, and in the 2008, Lee *et al.* reported some flavonoids were isolated from *T. scandens* stimulate glucose uptake in L6 myotubes, one of the causative agents for the tissue distraction and insulin resistance.

It is intended to provide an anti-diabetic drug containing active ingredient originating in natural plant which can be obtained and taken in daily diet, inhibits hyperglycemia after eating to thereby efficaciously relieve the onset of diabetes or the symptoms thereof, and is highly safe and less expensive. In conclusion, we have carried out a systematic investigation of some Vietnamese medicinal plants for PTP1B inhibitory activity. The results indicate a number of medicinal plants that may be useful for the treatment of diabetes, and provide the basis for further investigation on these medicinal plant species to isolate active constituents and drug development.

Acknowledgements

Mid-career Researcher Program through NRF grant funded by the MEST (2010-0000147) and Ministry of Health and Welfare (A000385).

References

Ahmad, F., Li, P.M., Meyerovitch, J., and Goldstein, B.J., Osmotic loading of neutralizing antibodies demonstrates a role for protein-0tyrosine phosphatase 1B in negative regulation of the insulin action pathway. *J. Biol. Chem*., **270**, 20503-20508 (1995).

Ahmed, I., Lakhani, M.S., Gillett, M., John, A., and Raza, H., Hypotriglyceridemic and hypocholesterolemic effects of anti- diabetic Momordica charantia (karela) fruit extract in streptozotocin-induced diabetic rats. *Diabetes Res. Clin. Pract*. **51**, 155-61 (2001).

Chattopadhyay, R.R., A comparative evaluation of some blood sugar lowering agents of plant origin. *J. Ethnopharmacol*. **67**, 367-372 (1999).

Chi, V.V., Dictionary of Vietnamese medicinal plants. Medical Publishing House, Hanoi, Vietnam (1997).

Cui, L., Na, M.K., Oh, H., Bae, E.Y., Jeong, D.G., Ryu. S.E., Kim. S., Kim, B.Y., Oha, W.K., and Ahna, J.S., Protein tyrosine phosphatase 1B inhibitors from Morus root bark. *Bioorg. Med. Chem. Lett*. **16**, 1426-1429 (2006).

Dat, N.T., Jin. X., Lee, K., Hong, Y.S., Kim, Y.H., and Lee, J.J., Hypoxia-Inducible Factor-1 Inhibitory Benzofurans and Chalcone-Derived Diels-Alder Adducts from *Morus* Species. *J. Nat. Prod*. **72**, 39-43 (2009).

Djang, A., Dietary supplement for promoting control of blood-sugar levels and associated pathology in type 2 diabetics. *PCT Int. Appl*. (2005)

Elchebly, M., Payette, P., michaliszyn, E., Cromlish, W., Collins, S., Loy, A.L., Normandin, D., Cheng, A., Himms-Hagen, J., Chan, C.C., Ranachandran, C., Gresser, M.J., Tremblay, M.L., and Kenedy, B.P., Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase 1B gene. *Science*, **283**, 1544-1548 (1999).

Grover, J.K. and Yadav, S.P., Pharmacological actions and potential uses of *Momordica charantia*: a review. *J. Ethnopharmacol*. **93**, 123-132 (2004).

Grover, J.K., Yadav, S., and Vats, V., Medicinal plants of India with antidiabetic potential. *J. Ethnopharmacol*. **81**, 81-100 (2002).

Hamaguchi, T., Sudo, T., and Osada, H., RK-682, a potent inhibitor of tyrosine phosphatase, arrested the mammalian cell cycle progression at G1phase. *FEBS Lett*. **372**, 54-58 (1995).

Haraguchi, H., Tanimoto, K., Tamura, Y., Mizutani, K., and Konoshita, T., Mode of antibacterial action of retrochalcones from *Glycyrrhiza inflata*. *Phytochemistry* **48**, 125-129 (1998).

Hoa, N.K., Norberg, A., Sillard, R., Dao, V.P., Thuan, N.D., Dzung, D.T. N., Jornvall, H., and Ostenson, C.G., The possible mechanisms by which phanoside stimulates insulin secretion from rat islets. *J. Endocrinol*. **192**, 389-394 (2007).

Hoang, D.M., Ngoc, T.M., Dat, N.T., Ha, D.T., Kim, Y.H., Luong, H.V., Ahn, J.S., and Bae, K.H., Protein Tyrosine Phosphatase 1B Constituent Inhibitors from *Morus bombycis*. *Bioorg. Med. Chem. Lett*. **19**, 6759-6761 (2009).

Johnson, T.O., Ermolieff, J., and Jirousek, M.R., Protein tyrosine phosphatase 1B inhibitors for diabetes. *Nat. Rev. Drug Discov*. **1**, 696-709 (2002).

Kenner, K., Anyanwu, E., Okefsky, J., and Kusari, J., Protein-tyrosine phosphatase 1B is a negative regulator of insulin- and insulin-like growth factor-I-stimulated signaling. *J. Biol. Hem*. **271**, 19810-19816 (1996).

Klaman, L.D., Boss, O., Peroni, O.D., Kim, J.K., Martino, J.L., Zabolotny, J.M., Moghal, N., Lubkin, M., Kim, Y.B., Sharpe, A.H., Stricker-Krongrad, A., Shulman, G.I., Nell, B.G, and Kahn, B.B., Increased energy expenditure, decreased adiposity and tissue-specific insulin sensitivity in protein tyrosine phosphatase 1B-deficient mice. *Mol. Cell. Biol*., **20**, 5479-5489 (2000).

Lee, M.S., Kim, C.H., Hoang, D.M., Kim, B.Y., Sohn, C.B., Kim, M.R., and Ahn, J.S., Genistein-derivatives from *Tetracera scandens* stimulate glucose-uptake in L6 myotubes. *Biol Pharm Bull*. **32**, 504-508 (2009).

Loi, D.T., Vietnamese Medicinal Plants and Ingredients. Medical Publishing House, Hanoi, Vietnam (2004).

Megalli, S., Davies, N.M., and Roufogalis, B.D., Anti-hyperlipidemic and hypoglycemic effects of *Gynostemma pentaphyllum* in the Zucker fatty rat. *J. Pharm. Pharm. Sci*. **9**, 281-291 (2006).

Meselhy, M.R., Kadota, S., Momose, Y., Hatakeyama, N., Kusai, A., Hattori, M., and Namba, T., Two new quinochalcone yellow pigments from *Carthamus tinctorius* and Ca^{2+} antagonistic activity of tinctormine. *Chem. Pharm. Bull*. **41**, 1796-1802 (1993).

Miura, T., Kako, M., Ishihara, E., Usami, M., Yano, H., Tanigawa, K., Sudo, K., and Seino, Y., Antidiabetic effect of Seishin-kanro-to in

KKAy mice. *Planta Med*. **63**, 320-322 (1997).
Na, M., Cui, L., Min, B.S., Bae, K., Yoo, J.K., Kim, B.Y., Oh, W.K., and Ahn, J.S., Protein tyrosine phosphatase 1B inhibitory activity of triterpenes isolated from Astilbe koreana, *Bioorg. Med. Chem. Lett*. **16**, 3273-3276 (2006).
Nakagawa, K., Kishida, H., Arai, N., Nishiyama, T., and Mae, T., Licorice flavonoids suppress abdominal fat accumulation and increase in blood glucose level in obese diabetic KK-Ay mice. *Biol. Pharm. Bull*. **27**, 1775-1778 (2004).
Ngo, H.N., Teel, R.W., and Lau, B.H. S., Modulation of mutagenesis, DNA binding, and metabolism of aflatoxin B_1 by licorice compounds. *Nutrition Res*. **12**, 247-257 (1992).
Nishino, H., Yoshioka, K., Iwashima, A., Takizawa, H., Konishi, S., Okamoto, H., Okabe, H., Shibata, S., Fujiki, H., and Sugimura, T., Glycyrrhetic-Acid inhibits tumor-promoting activity of teleocidin and 12-*O*-tetradecanoylphorbol-13-acetate in two-stage mouse skin carcinogenis. *Japan. J. Cancer Res*. **77**, 33-38 (1986).
Nomura, T., Fukai, T., Hano, Y., and Urano, S., Constituents of the Chinese Crude Drug "Sāng-Bái-Pí" (Morus Root Bark). *Planta Med*. **47**, 95-99 (1983).
Norberg, A., Hoa, N.K., Liepinsh, E., Phan, D.V., Thuan, N.D., Joernvall, H., Sillard, R., and Oestenson, C.G., A Novel Insulin-releasing substance, phanoside, from the plant *Gynostemma pentaphyllum*. *J. Biol. Chem*. **279**, 41361-41367 (2004).
Nose, M., Fujimoto, T., Takeda, T., Nishibe, S., and Ogihara, Y., Structural transformation of lignan compounds in rat gastrointestinal tract. *Planta Med*. **58**, 520-523 (1992).
Nose, M., Ito, M., Kamimura, K., Shimizu, M., and Ogihara, Y., A comparison of the antihepatotoxic activity between glycyrrhizin and glycyrretic acid. *Planta Med*. **60**, 136-139 (1994).
Satoru, K., Tsumoru, W., Satoshi, M., Kaori, F., Junichi, O., and Shigeru, M., Antidiabetic compositions containing safflower extracts. *PCT Int. Appl*. p. 22 (2005).
Schroder, G., Wehinger, E., Lukacin, R., Wellmann, F., Seefelder, W., Schwab, W., and Schroder, L., Flavonoid methylation: a novel 4-Omethyltransferase from *Catharanthus roseus*, and evidence that partially methylated flavanones are substrates of four different (2004).
Seely, B., Staubs, P., Reichart, D., Berhanu, P., Milarsky, K., Saltiel, K., Kusari, J., and Olefsky, J., Protein tyrosine phosphatase 1B interacts with the activated insulin receptor. *Diabetes*, **45**, 1379-1385 (1996).
Shi, Y.Q., Fukai, T., Sakagami, H., Chan, W.J., Yang, P.Q., Wang, F.P., and Nomura, T., Cytotoxic Flavonoids with Isoprenoid Groups from *Morus mongolica*. *J. Nat. Prod*. **64**, 181-188 (2001).
Singh, S.N., Vats, P., Suri, S., Shyam, R., Kumria, M.M.L., Ranganathan, S., and Sridharan, K., Effect of an antidiabetic extract of *Catharanthus roseus* on enzymic activities in streptozotocin induced diabetic rats. *J. Ethnopharmacol*. **76**, 269-277 (2001).
Sohn, H.Y., Son, K.H., Kwon, C.S., Kwon, G.S., and Kang, S.S., Antimicrobial and cytotoxic activity of 18 prenylated flavonoids isolated from medicinal plants: *Morus alba* L., *Morus mongolica* Schneider, *Broussnetia papyrifera* (L.) Vent, *Sophora flavescens* Ait and *Echinosophora koreensis* Nakai. *Phytomedicine*. **11**, 666-672 (2004).
Takagi, K. and Ishii, Y., New coumarins isolated from the roots of some plant extracts such as *Glycyrrhiza glabra*. *Arzneim. Forsh,* **17**, 1544-1547 (1967).
Tonks, N.K., PTP1B: From the sidelines to the front lines. *FEBS Lett*. **546**, 140-148 (2003).
Vietnam National Diabetes Federation Conference, June 23, (2003).
Wang, W.Q., Sun, J.P., and Zhang, Z.W., An overview of the protein tyrosine phosphatase superfamily. *Curr. Top. Med. Chem*., **3**, 739-748 (2003).
Welihinda, J., Karunanayake, E.H., Sheriff, M.H., and Jayasinghe, K.S., Effect of *Momordica charantia* on the glucose tolerance in maturity onset diabetes. *J. Ethnopharmacol*. **17**, 277-282 (1986).
White, F. and Rafique, G., Diabetes prevalence and projections in South Asia. *The Lancet* **360**, 804-805 (2002).
Xie, L., Lee, S.Y., Andersen, J.N., Waters, S., Shen, K., Guo, X.L., Moller, N.P., Olefsky, J.M., Lawrence, D.S., and Zhang, Z.Y., Cellular effects of small meleclue PTP1B inhibitors on insulin signaling. *Biochemistry*, **42**, 12792-12804 (2003).
Zani, F., Cuzzoni, M.T., Daglia, M., Benvenuti, S., Vampa, G., and Mazza, P., Mutual interactions among ingredients of betel quid in inducing genotoxicity on Chinese hamster ovary cells. *Planta Med*. **59**, 502-507 (1993).
Zhang, R., Zhou, J., Jia, Z., Zhang, Y., and Gu, G., Hypoglycemic effect of *Rehmannia glutinosa* oligosaccharide in hyperglycemic and alloxan-induced diabetic rats and its mechanism. *J. Ethnopharmacol*. **90**, 39-43 (2004).
Zinker, B.A., Rondinone, C.M., Trevillyan, J.M., Gum, R.J., Clampit, J.E., Waring, J.F., Xie, N., Wilcox, D., Jacobson, P., Frost, L., Kroeger, P.E., Reilly, R.M., Kotersky, S., Ppgenorth, T.J., Ulrich, R.G., Crossby, S., Butler, M., Murray, S.F., Mckay, R.A., Bhanot, S., Monia, B.P., and Jirousek, M.R., PTP1B antisense oligonucleotide lowers PTP1B protein, normalizes blood glucose, and improves insulin sensitivity in diabetic mice. *Proc. Natl. Acad. Sci. USA*, **99**, 11357-11362 (2002).

Received September 6, 2010
Revised October 23, 2010
Accepted October 28, 2010