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Screening for Anti-diabetic Effects of Prescribed Korean Traditional Medicines

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Abstract - Herb extracts commercially used in Korea were screened for PPAR-γ agonist test and α-glucosidase inhibition assay. Total 16 herb plants had a PPAR-γ agonist activity. Specially, *Alisma orientale* Juz (108.41%), *Ephedra sinica* (98.22%), *Sasa japonica* Makino var. *purpurascens* Nakai (140.68%), *Astragalus membranaceus* Bunge (106.79%) and *Cnidium officinale* Makino (113.00%) showed high PPAR-γ agonist activity rate compared with rosiglitazone's (167.46%). And *Cornus officinalis* S. et Z. (90.3%), *Cinnamomum cassia* Blume (89.2%), *Psoralea corylifolia* L. (89.8%), *Paeonia japonica* (Makino) Miyabe (92.4%) and *Paeonia suffruticosa* Andr (93.2%), showed high α-glucosidase inhibition rates. These results support previous reports of the efficacy of Oriental medicinal plants used for diabetes mellitus.

Key words - Korean traditional medicine, Screening, PPAR-γ agonist, α-Glucosidase inhibition, Diabetes mellitus

Introduction

The incidence of type II diabetes mellitus (T2DM) has reached epidemic proportions in western and developing countries, with an estimated 194 million people afflicted. Peripheral insulin resistance is a key feature of T2DM and results from a combination of sedentary lifestyle, unhealthy dietary habits, and genetic predisposition (Skyler, 2004). Insulin resistance is also implicated in a number of life threatening disorders collectively referred to as the metabolic syndrome (Hansen, 1999). T2DM affects many metabolic pathways in different tissues, many of which are potential targets for drug treatment (van de Venter *et al*., 2008). Type II diabetes is characterized by hepatic and peripheral (muscle and adipose tissue) insulin resistance. The pancreas compensates by secreting more insulin, but eventually the beta cells will fail to sustain this (Cerasi, 2000), at which stage the patient requires insulin treatment. During the stage when insulin is still produced, various other classes of drugs, in combination with lifestyle alterations, can be used to manage the disease (Matthaei *et al*., 2000). These drugs act through a number of different ways or targets to reduce blood glucose levels. When screening for an anti-diabetic agent, it is important to include as many of these targets as possible to ensure that possible 'hits' are not excluded (van de Venter *et al*., 2008).

PPARs (peroxisome proliferator-activated receptors), the ligand-activated nuclear transcription factors, regulate the gene expression of adipocyte differentiation, lipogenesis, and glucose metabolism, and are involved in type 2 diabetes, dyslipidemia, atherosclerosis, obesity, and other metabolic diseases (Evans *et al*., 2004; Pakala *et al*., 2004). Ligands of PPARs have been used for treating these diseases clinically for decades (Huang *et al*., 2006). The thiazolidinedione class of insulin-sensitizing compounds such as rosiglitazone and pioglitazone, which lower hyperglycemia, is PPAR-γ agonists (Stales and Fruchart, 2005). However, the limitations and the side-effects of these drugs have driven researchers to look for a new type of drug that could be of benefit for the treatment of some of these metabolic disorders.

3T3-L1 fibroblasts transformed to adipocyte when differenti-

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ation inducer like insulin, dexamethasone and IBMX (3-Isobutyl-1-methylxanthine) are added (Gerhold *et al*., 2002), but this mechanism has not been known clearly yet. Known mechanisms is that adipocyte differentiation is starting to be expressed when the transcription factors which operate in genes at fatty tissues specifically is expressed. This transcription factors are peroxisome proliferator-activated receptor γ (PPAR-γ), CCAAT/ enhancing binding protein (C/EBP), adipocyte differentiation and determinator factor 1 and sterol regulatory element binding protein 1c. It is known that substance induced differentiation can convert fibroblast to adipocyte by promoting expressing of these transcription factors. Especially PPAR-γ is able to control the cell growth, start converting of adipocyte, and regulate the adipocyte differentiation. Also C/EBP is expressed in adipocyte and C/EBP helps the PPAR-γ convert preadipocyte to adipocyte (Yamamoto *et al*., 2002). Therefore, it is considered that the herb plants, which can differentiate 3T3-L1 fibroblast and increase the lipid accumulation, are able to act as a PPAR-γ agonist.

Current medication options for the treatment of diabetes are relatively limited, have non-negligible side effects, and must often be prescribed in combination (Cheng and Fantus, 2005). The use of natural health products as complementary or alternative approaches to existing medications is growing in popularity. While these have been the object of very few rigorous scientific studies, it is clear that many plants possess hypoglycemic activity, some having considerable anti-diabetic potential (Marles and Farnsworth, 1995). The prevalence of use of complementary and alternative medicine (CAM) is high among people with diabetes (Wolsko *et al*., 2002) and those seeking to prevent chronic diseases that include diabetes (Harnack *et al*., 2001).

Active ingredient of medicinal plants that make Korea herb medicine is secondary metabolites with bioactive substances. Recently insulin like substances from medicinal plants as secondary metabolites, attention has been separated. It has been reported that royal jelly effects on the prevention and treatment of diabetes, because trans-10-hydroxy-2-decanoic acid in royal jelly is insulin like substance (Kameda *et al*., 1996). Also, It has been reported that bakuchiol from *Ortholobium pubescens* (which is a traditional medicinal plants in Peru) is insulin material (Krenisky *et al*., 1999).

In Korea, a traditional medicine, diabetes mellitus could be divided in “So-gal”, “So-joong” and “So-sin” broadly and it has been evaluated that So-gal part in Donguibogam is described in detail as these day’s diabetes mellitus, and it is amazing. Also, in Asia including Korea, various herbs have been used for treatment of diabetes mellitus. Some studies had found out the anti-diabetic effects of theses herbs, but there are not enough evidences of their anti-diabetic effects.

In this study, we screened the frequent medicinal herbs in Korea traditional medical book, “Donguibogam” by PPAR-γ agonist test and α-glucosidase inhibition assay.

Materials and Methods

Literature search

We had researched the Korea traditional medical book, “Donguibogam”, and found out the prescription (Table 1) and frequent herbs (Table 2). There were total 54 Korea

Table 1. Korean traditional herb medicines used for treating diabetes in Donguibogam

Herbmed	Prescription
Backhogainsamtang	*Gypsum, Anemarrhena asphodeloides* Bunge, *Glycyrrhiza uralensis* Fisch, *Oryza sativa L., Panax ginseng* C. A. Meyer
Bosinjihwangwon	*Phellodendron amurense* Rupr., *Rehmannia glutinosa* Libosch., *Poria cocos* Wolf, *Rehmannia glutinosa* Libosch., *Asparagus cochinchinensis Merr., Panax ginseng* C. A. Meyer, *Chrysanthemum indicum* L., *Scutellaria baicalensis* Georgi, *Angelica gigas* Nakai, *Citrus aurantium* L., *Liriope platyphylla* Wang. et Tang, *Scutellaria baicalensis* Georgi
Cheongsimyeonjaeum	*Nelumbo nucifera* Gaertn, *Poria cocos* Wolf, *Panax ginseng* C. A. Meyer, *Astragalus membranaceus* Bunge, *Scutellaria baicalensis* Georgi, *Plantago asiatica* L., *Liriope platyphylla* Wang. et Tang, *Lycium chinense* Mill., *Glycyrrhiza uralensis* Fisch

Table 1. Continued

Herbmed	Prescription
Cheongsinbogitang	*Cimicifuga heracleifolia* Kom., *Bupleurum falcatum* L., *Angelica gigas* Nakai, *Schizonepeta tenuifolia* Briq, *Sinomenium acutum* Rehder et E. H. Wilson, *Prunus persica* (L.) Batsch, *Phellodendron amurense* Rupr., *Coptis japonica* Makino, *Anemarrhena asphodeloides* Bunge, *Glycyrrhiza uralensis* Fisch, *Gypsum, Rehmannia glutinosa* Libosch., *Asarum heterotropoides* F. *Maekawa, Prunus armeniaca L. var. ansu* Maxim, *Zanthoxylum bungeanum* , *Carthamus tinctorius* L.
Cheonwhasan	*Trichosanthes kirilowii* Maxim, *Rehmannia glutinosa* Libosch., *Pueraria lobata* (Willd.) Ohwi, *Liriope platyphylla* Wang. et Tang, *Schizandra chinensis* Bailon, *Glycyrrhiza uralensis* Fisch
Dahwanggamchoeumja	*Rheum undulatum* L., *Glycyrrhiza uralensis* Fisch, *Glycine semen*
Eegwonsan	*Talcum, Glycyrrhiza uralensis* Fisch
Gagambackchulsan	*Pueraria lobata* (Willd.) Ohwi, *Panax ginseng* C. A. Meyer, *Atractylodes japonika* Koidz., *Poria cocos* Wolf, *Aucklandia lappa Decne.*, *Anemarrhena asphodeloides* Bunge, *Phellodendron amurense* Rupr., *Glycyrrhiza uralensis* Fisch, *Schizandra chinensis* Bailon
Gagambackhotang	*Gypsum, Anemarrhena asphodeloides* Bunge, *Panax ginseng* C. A. Meyer, *Phellodendron amurense* Rupr., *Scrophularia buergeriana* Miq., *Glycyrrhiza uralensis* Fisch, *Schizandra chinensis* Bailon, *Oryza sativa* L.
Gagamsingihwan	*Rehmannia glutinosa* Libosch., *Paeonia suffruticosa* Andr, *Poria cocos* Wolf, *Cornus officinalis* S. et Z., *Schizandra chinensis* Bailon, *Alisma orientale* Juz., *Cervus nippon* hortulorum, *Dioscorea batatas* Decne., *Cinnamomum cassia* Blume, *Aquilaria agallocha Roxb.*
Gamijeonssibackchoolsan	*Pueraria lobata* (Willd.) Ohwi, *Panax ginseng* C. A. Meyer, *Atractylodes japonika* Koidz., *Poria cocos* Wolf, *Agastache rugosa* (Fisc.r et Mey.) Kuntze, *Glycyrrhiza uralensis* Fisch, *Aucklandia lappa* Decne., *Bupleurum falcatum* L., *Citrus aurantium* L., *Schizandra chinensis* Bailon
Gangsimtang	*Trichosanthes kirilowii* Maxim, *Panax ginseng* C. A. Meyer, *Polygala tenuifolia* Willd, *Angelica gigas* Nakai, *Rehmannia glutinosa* Libosch., *Poria cocos* Wolf, *Astragalus membranaceus* Bunge, *Schizandra chinensis* Bailon, *Glycyrrhiza uralensis* Fisch, *Zizyphus jujuba var. inermis*
Goryuntang	*Melia azedarach, Moschus moschiferus*
Hwahyulikgitang	*Phellodendron amurense* Rupr., *Cimicifuga heracleifolia* Kom., *Rehmannia glutinosa* Libosch., *Coptis japonica* Makino, *Gypsum, Prunus armeniaca L. var. ansu* Maxim, *Prunus persica* (L.) Batsch, *Anemarrhena asphodeloides* Bunge, *Sinomenium acutum* Rehder et E. H. Wilson, *Ostericum koreana* Kitagawa, *Angelica gigas* Nakai, *Bupleurum falcatum* L., *Ephedra sinica, Glycyrrhiza uralensis* Fisch, *Carthamus tinctorius* L.
Hyuntodan	*Cuscuta chinensis* Lamark, *Schizandra chinensis* Bailon, *Poria cocos* Wolf, *Nelumbo nucifera* Gaertn, *Dioscorea batatas* Decne.
Insambockreyngsan	*Talcum, Gypsum rubrum, Glycyrrhiza uralensis* Fisch, *Poria cocos* Wolf, *Pueraria lobata* (Willd.) Ohwi, *Scutellaria baicalensis* Georgi, *Mentha arvensis var. piperascens* MALINV, *Rheum undulatum* L., *Forsythia viridissima* Lindley, *Panax ginseng* C. A. Meyer, *Atractylodes japonika* Koidz., *Alisma orientale* Juz., *Platycodon grandiflorum* A. DC, *Gardenia jasminoides* Ellis, *Trichosanthes kirilowii* Maxim, *Amomum villosum* Lour.
Insamsan	*Talcum, Gypsum rubrum, Glycyrrhiza uralensis* Fisch, *Gypsum, Panax ginseng* C. A. Meyer

Table 1. Continued

Herbmed	Prescription
Insamseokgotang	*Gypsum, Anemarrhena asphodeloides* Bunge, *Panax ginseng* C. A. Meyer, *Glycyrrhiza uralensis* Fisch
Jaeumyangyoungtang	*Angelica gigas* Nakai, *Panax ginseng* C. A. Meyer, *Rehmannia glutinosa* Libosch., *Liriope platyphylla* Wang. et Tang, *Paeonia japonica* (Makino) Miyabe, *Anemarrhena asphodeloides* Bunge, *Phellodendron amurense* Rupr., *Glycyrrhiza uralensis* Fisch, *Schizandra chinensis* Bailon
Joosahwangreonwon	*Coptis japonica* Makino, *Rehmannia glutinosa* Libosch., *Cinnabaris*
Macmoondongeumja	*Liriope platyphylla* Wang. et Tang, *Anemarrhena asphodeloides* Bunge, *Trichosanthes kirilowii* Maxim, *Panax ginseng* C. A. Meyer, *Schizandra chinensis* Bailon, *Pueraria lobata* (Willd.) Ohwi, *Poria cocos* Wolf, *Rehmannia glutinosa* Libosch., *Glycyrrhiza uralensis* Fisch, *Sasa japonica Makino var. purpurascens* Nakai
Meahwatang	*Oraza sativa* L. *var. glutinosa, Matsumura, Morus alba* Linne
Moondongeumja	*Liriope platyphylla* Wang. et Tang, *Schizandra chinensis* Bailon, *Panax ginseng* C. A. Meyer, *Lycium chinense* Mill., *Poria cocos* Wolf, *Glycyrrhiza uralensis* Fisch
Nahaeumja	*Gypsum, Anemarrhena asphodeloides* Bunge, *Glycyrrhiza uralensis* Fisch, *Ledebouriella seseloides* (Hoffm.) Wolff, *Panax ginseng* C. A. Meyer., *Forsythia viridissima* Lindley, *Amomum cardamomum* L., *Platycodon grandiflorum* A. DC, *Cimicifuga heracleifolia* Kom., *Pinellia ternata* Breitenbach, *Zingiber officinale* Roscoe
Nockyounghwan	*Liriope platyphylla Wang. et Tang, Cervus nippon hortulorum, Rehmannia glutinosa* Libosch., *Astragalus membranaceus* Bunge, *Schizandra chinensis* Bailon. *Gallus gallus var.* domesticus, *Cistanche deserticola* Y.C. Ma, *Cornus officinalis* S. et Z., *Psoralea corylifolia* L., *Achyranthes bidentata* Blume, *Panax ginseng* C. A. Meyer, *Poria cocos* Wolf, *Lycium chinense* Mill., *Scrophularia buergeriana* Miq.
Ockcheonsan	*Trichosanthes kirilowii* Maxim, *Pueraria lobata* (Willd.) Ohwi, *Liriope platyphylla* Wang. et Tang, *Rehmannia glutinosa* Libosch., *Schizandra chinensis* Bailon, *Glycyrrhiza uralensis* Fisch, *Oraza sativa* L. var. *glutinosa* Matsumura
Ockcheonwhan	*Trichosanthes kirilowii* Maxim,*Pueraria lobata* (Willd.) Ohwi, *Liriope platyphylla* Wang. et Tang, *Panax ginseng* C. A. Meyer, *Poria cocos* Wolf, *Astragalus membranaceus* Bunge, *Prunus mume Siebold et* Zucc., *Glycyrrhiza uralensis* Fisch
Odootang	*Pueraria lobata* (Willd.) Ohwi, *Dryopteris crassirhizoma* NAKAI, *Glycyrrhiza uralensis* Fisch, *Glycine semen, Glycine max* Merrill, *Vigna radiata* (L.) R. Wilczek., *Phaseolus angularis* W. F. WIGHT.
Ojeubockcheonwhan	*Coptis japonica* Makino, *Pueraria lobata* (Willd.) Ohwi, *Trichosanthes kirilowii* Maxim, *Anemarrhena asphodeloides* Bunge, *Liriope platyphylla* Wang. et Tang, *Schizandra chinensis* Bailon, *Panax ginseng* C. A. Meyer, *Rehmannia glutinosa* Libosch., *Prunus mume* Siebold et Zucc., *Nelumbo nucifera* Gaertn, *Angelica gigas* Nakai, *Glycyrrhiza uralensis* Fisch
Omeamogwatang	*Prunus mume* Siebold et Zucc., *Chaenomeles sinensis* Koehne., *Hordeum vulgare* L., *Amomum tsao-ko* Crevost et Lemarie, *Glycyrrhiza uralensis* Fisch
Palmisingiwhan	*Rehmannia glutinosa* Libosch., *Dioscorea batatas* Decne., *Cornus officinalis* S. et Z., *Alisma orientale* Juz., *Paeonia suffruticosa* Andr, *Poria cocos* Wolf, *Schizandra chinensis* Bailon, *Cinnamomum cassia* Blume

Table 1. Continued

Herbmed	Prescription
Saengjingamrotang	*Gypsum, Gentiana scabra* Bunge, *Phellodendron amurense* Rupr., *Bupleurum falcatum* L., *Ostericum koreana* Kitagawa, *Astragalus membranaceus* Bunge, *Anemarrhena asphodeloides* Bunge, *Scutellaria baicalensis* Georgi, *Angelica gigas* Nakai, *Cimicifuga heracleifolia* Kom., *Ledebouriella seseloides* (Hoffm.) Wolff, *Sinomenium acutum* Rehder et E. H. Wilson, *Rehmannia glutinosa* Libosch., *Glycyrrhiza uralensis* Fisch, *Prunus armeniaca* L. var. ansu Maxim,*Prunus persica* (L.) Batsch, *Carthamus tinctorius* L.
Saengjinyanghyeltang	*Angelica gigas* Nakai, *Paeonia japonica (*Makino) Miyabe, *Rehmannia glutinosa* Libosch., *Liriope platyphylla* Wang. et Tang, *Cnidium officinale* Makino, *Coptis japonica* Makino, *Trichosanthes kirilowii* Maxim, *Anemarrhena asphodeloides* Bunge, *Phellodendron amurense* Rupr., *Nelumbo nucifera* Gaertn, *Prunus mume* Siebold et Zucc., *Mentha arvensis var. piperascens* MALINV., *Glycyrrhiza uralensis* Fisch
Samooltang	*Rehmannia glutinosa* Libosch., *Paeonia japonica* (Makino) Miyabe, *Cnidium officinale* Makino, *Angelica gigas* Nakai
Samsohwan	*Coptis japonica* Makino, *Liriope platyphylla* Wang. et Tang, *Pueraria lobata* (Willd.) Ohwi
Sangbaekpitang	*Morus alba* Linne, *Poria cocos* Wolf, *Panax ginseng* C. A. Meyer, *Liriope platyphylla* Wang. et Tang, *Pueraria lobata* (Willd.) Ohwi, *Dioscorea batatas* Decne., *Cinnamomum cassia* Blume, *Glycyrrhiza uralensis* Fisch
Seangjihwangeuja	*Panax ginseng* C. A. Meyer, *Rehmannia glutinosa* Libosch., *Astragalus membranaceus* Bunge, *Asparagus cochinchinensis* Merr., *Liriope platyphylla* Wang. et Tang, *Citrus aurantium* L., *Dendrobium nobile* Lindl., *Eriobotrya japonica* (Thunb.) Lindley, *Alisma orientale* Juz.
Seangjihwanggo	*Rehmannia glutinosa* Libosch., *pis indiraRadoszkowski, Poria cocos* Wolf, *Panax ginseng* C. A. Meyer.
Seokjajenitang	*Japanese lady bell , Gypsum, Panax ginseng* C. A. Meyer ,*Poria cocos* Wolf, *Trichosanthes kirilowii* Maxim, *Magenetitum, Anemarrhena asphodeloides* Bunge, *Pueraria lobata* (Willd.) Ohwi, *Scutellaria baicalensis* Georgi, *Glycyrrhiza uralensis* Fisch, *Sus scrofa var. domesticus, Glycine semen*
Singihwan	*Rehmannia glutinosa* Libosch., *Dioscorea batatas* Decne., *Cornus officinalis* S. et Z., *Alisma orientale* Juz., *Paeonia suffruticosa* Andr, *Poria cocos* Wolf, *Schizandra chinensis* Bailon
Soongisan	*Magnolia officinalis* Rehder et Wilson, *Rheum undulatum* L., *Poncirus trifoliata* Rafinesqul
Wesangcheonwhawon	*Coptis japonica* Makino, *Dolichos lablab* L, *Aloe vera* L. , *Cinnabaris, Poria cocos* Wolf, *Ostrea gigas* Thunb, *Anemarrhena asphodeloides* Bunge, *Sophora flavescens* Ait, *Trichosanthes kirilowii* Maxim
Whalhyulyunjosangjineum	*Asparagus cochinchinensis* Merr., *Liriope platyphylla* Wang. et Tang, *Schizandra chinensis* Bailon, *Trichosanthes kirilowii* Maxim, *Cannabis sativa, Angelica gigas* Nakai, *Rehmannia glutinosa* Libosch., *Trichosanthes kirilowii* Maxim, *Glycyrrhiza uralensis* Fisch
Whanggeumtang	*Scutellaria baicalensis* Georgi, *Gardenia jasminoides* Ellis, *Platycodon grandiflorum* A. DC, *Liriope platyphylla* Wang. et Tang, *Angelica gigas* Nakai, *Rehmannia glutinosa* Libosch., *Trichosanthes kirilowii* Maxim, *Pueraria lobata* (Willd.) Ohwi, *Panax ginseng* C. A. Meyer, *Paeonia japonica* (Makino) Miyabe, *Prunus mume* Siebold et Zucc.
Whanggitang	*Rehmannia glutinosa* Libosch., *Astragalus membranaceus* Bunge, *Poria cocos* Wolf, *Trichosanthes kirilowii* Maxim, *Liriope platyphylla* Wang. et Tang, *Schizandra chinensis* Bailon, *Glycyrrhiza uralensis* Fisch

Table 1. Continued

Herbmed	Prescription
Whangryonjiwhangtang	*Coptis japonica* Makino, *Rehmannia glutinosa* Libosch., *Trichosanthes kirilowii* Maxim, *Schizandra chinensis* Bailon, *Angelica gigas* Nakai, *Panax ginseng* C. A. Meyer, *Pueraria lobata* (Willd.) Ohwi, *Poria cocos* Wolf, *Liriope platyphylla* Wang. et Tang, *Glycyrrhiza uralensis* Fisch, *Zingiber officinale* Roscoe, *Zizyphus jujuba var.* inermis,*Sasa japonica Makino var. purpurascens* Nakai
Whangryunjeodoowhan	*Sus scrofa var.* domesticus, *Coptis japonica* Makino, *Triticum aestivum* L., *Trichosanthes kirilowii* Maxim, *Poria cocos* Wolf, *Liriope platyphylla* Wang. et Tang
Whangryunjeodoowhan	*Sus scrofa var, Coptis japonica* Makino, *Liriope platyphylla* Wang. et Tang, *Anemarrhena asphodeloides* Bunge, *Trichosanthes kirilowii* Maxim
Whanhgiyuckiltang	*Astragalus membranaceus* Bunge, *Glycyrrhiza uralensis* Fisch
Woozeumgo	*Rehmannia glutinosa* Libosch., *Bos taurus coreannae, Coptis japonica* Makino, *Trichosanthes kirilowii* Maxim, *Zingiber officinale* Roscoe, *Apis indira* Radoszkowski
Yeojigo	*Bos taurus var. domesticus* Gmelin, *Apis indira* Radoszkowski, *Prunus mume* Siebold et Zucc., *Zingiber officinale* Roscoe, *Moschus moschiferus*
Yindongwon	*Lonicera japonica* Thunb.
Yongbongwon	*Dioscorea batatas* Decne., *Cuscuta chinensis* Lamark, *Cervus nippon hortulorum*
Yukmigeehwanghwan	*Rehmannia glutinosa* Libosch., *Dioscorea batatas* Decne., *Cornus officinalis* S. et Z., *Alisma orientale* Juz., *Paeonia suffruticosa* Andr, *Poria cocos* Wolf

Table 2. Selective anti-diabetes effects of 50% EtOH extracts of Oriental herbs and frequency of herbs in prescription of Donguibogam

Plant species	Plant part	Korean name	Frequency	PPAR-γ agonist activity (%)		α-glucosidase inhibition rate (%)
				100 ㎍/ml	50 ㎍/ml	
Alismataceae						
Alisma orientale Juz.	Rhizome	Tacksa	4	-	108.41±11.12	-
Amaranthaceae						
Achyranthes bidentata Blume	Root	Wooseul	1	-	-	-
Araceae						
Pinellia ternata Ten. et Breittenb.	Tuber	Banha	1	-	-	-
Araliaceae						
Panax ginseng C. A. Meyer.	Root	Insam	23	-	-	64.8
Aristolochiaceae						
Asarum heterotropoides F. Maekawa	Root	Seshin	1	-	-	-
Campanulaceae						
Platycodon grandiflorum A. DC.	Root	Gilgyung	3	-	-	-
Caprifoliaceae						
Lonicera japonica Thunb.	Leaf, stem	Indong	1	-	-	-

Table 2. Continued

Plant species	Plant part	Korean name	Frequency	PPAR-γ agonist activity (%)		α-glucosidase inhibition rate (%)
				100 μg/ml	50 μg/ml	
Compositae						
Atractylodes japonika Koidz.	Rhizome	Backchul	3	-	44.56±11.65	37.7
Aucklandia lappa Decne.	Root	Mockhyang	2	-	-	-
Carthamus tinctorius L.	Flower	Honghwa	3	-	-	-
Chrysanthemum indicum L.	Flower	Gamgook	1	-	-	-
Convolvulaceae						
Cuscuta chinensis Lamark	Seed	Tosaja	2	-	-	85.3
Cornaceae						
Cornus officinalis S. et Z.	Fruit	Sansooyou	4	-	-	90.3
Cucurbitaceae						
Trichosanthes kirilowii Maxim	Seed	Gwarooin	1	-	-	-
Trichosanthes kirilowii Maxim	Root	Cheonhwaboon	17	-	-	-
Dioscoreaceae						
Dioscorea batatas Decne.	Rhizome	Sanyack	7	-	-	-
Ephedraceae						
Ephedra sinica	Root	Mahwangguen	1	69.95±0.97	98.22±9.64	89.5
Gentianaceae						
Gentiana scabra Bunge	Root	Yongdamcho	1	-	-	15.6
Gramineae						
Hordeum vulgare L.	Fruit	Meacka	1	-	-	-
Sasa japonica Makino var. *purpurascens* Nakai	Leaf	Joockyeop	2	78.69±5.79	140.68±72.28	67.6
Triticum aestivum L.	Fruit	Boosomeack	2	-	-	-
Labiatae						
Agastache rugosa (Fisc.r et Mey.) Kuntze	Whole	Gwackhyang	1	72.65±14.30	76.20±7.03	65.7
Cinnamomum cassia Blume	Cortex	Gyepea	1	-	-	89.2
Schizonepeta tenuifolia Briq.	Spica	Hyunggea	1	-	-	28.4
Scutellaria baicalensis Georgi	Root	Hwanggeum	6	-	-	-
Leguminosae						
Astragalus membranaceus Bunge	Root	Hwanggy	8	83.58±14.91	106.79±19.86	-
Dolichos lablab L.	Seed	BackPyendoo	1	-	-	-
Glycyrrhiza uralensis Fisch	Root	Gamcho	32	-	-	62.4
Psoralea corylifolia L.	Seed	Pagogee	1	-	-	89.8
Pueraria lobata (Willd.) Ohwi	Root	Galguen	14	-	-	30.7
Sophora flavescens Ait.	Root	Gosam	1	-	-	60.5
Liliaceae						
Anemarrhena asphodeloides Bunge	Rhizome	Geemo	15	-	-	-
Asparagus cochinchinensis Merr.	Tuber	Cheonmoondong	3	17.48±8.28	25.70±9.61	-
Liriope platyphylla Wang. et Tang	Tuber	Makcmoondong	20	-	-	-

Table 2. Continued

Plant species	Plant part	Korean name	Frequency	PPAR-γ agonist activity (%)		α-glucosidase inhibition rate (%)
				100 μg/ml	50 μg/ml	
Magnoliaceae						
Magnolia officinalis Rehder et Wilson	Cortex	Hoobark	1	-	-	84.9
Menispermaceae						
Sinomenium acutum Rehder et E. H. Wilson	Rhizome	Banggi	3	-	-	47.1
Moraceae						
Cannabis sativa	Seed	Majainn	1	-	-	-
Nymphaeaceae						
Nelumbo nucifera Gaertn.	Seed	Younja	4	-	-	37.6
Orchidaceae						
Dendrobium nobile Lindl.	Whole	Seockgock	1	-	-	50.5
Orobanchaceae						
Cistanche deserticola Y.C. Ma	Whole	Yoouckjongyong	1	15.57±26.95	27.65±20.00	29.2
Ostreidae						
Ostrea gigas Thunb.	Testa	Morea	1	-	-	37.2
Paeoniaceae						
Paeonia japonica (Makino) Miyabe	Root	Beackjackyack	4	-	-	92.4
Paeonia suffruticosa Andr.	Root cortex	Mockdanpea	4	14.12±21.54	73.47±1.86	93.2
Plantaginaceae						
Plantago asiatica L.	Seed	Chajeonja	1	-	-	-
Polygalaceae						
Polygala tenuifolia Willd.	Root	Wonjea	1	-	-	87.8
Polygonaceae						
Rheum undulatum L.	Rhizome	Deahwang	3	17.85±60.86	32.91±2.92	-
Polyporaceae						
Poria cocos Wolf	Hoelen	Backbokryuong	16	90.84±1.37	-	-
Ranunculaceae						
Cimicifuga heracleifolia Kom.	Rhizome	Seungma	4	21.82±8.78	68.90±4.90	54.7
Coptis japonica Makino	Rhizome	Hwangryun	11	19.54±6.93	24.51±16.76	-
Rosaceae						
Chaenomeles sinensis Koehne.	Fruit	Mogwa	1	-	-	85.6
Eriobotrya japonica (Thunb.) Lindley	Leaf	Beepayeop	1	-	-	81.5
Prunus armeniaca L. var. *ansu* Maxim.	Seed	Hangin	3	-	-	-
Prunus mume Siebold et Zucc.	Fruit	Omea	6	-	-	-
Prunus persica (L.) Batsch.	Seed	Doin	3	-	-	-
Rubiaceae						
Gardenia jasminoides Ellis	Fruit	Cheeja	2	-	-	26.7
Rutaceae						
Citrus aurantium L.	Fruit	Jeegack	3	-	-	44.6
Phellodendron amurense Rupr.	Cortex	Hwangbeack	8	-	-	39.6

Table 2. Continued

Plant species	Plant part	Korean name	Frequency	PPAR-γ agonist activity (%)		α-glucosidase inhibition rate (%)
				100 μg/ml	50 μg/ml	
Poncirus trifoliata Rafinesqul	Fruit	Jeeseal	1	32.33±12.03	38.47±19.07	71.0
Zanthoxylum bungeanum	Fruit	Cheoncho	1	-	-	57.0
Schisandraceae						
Schizandra chinensis Bailon	Fruit	Omija	18	-	-	-
Scrophulariaceae						
Rehmannia glutinosa Libosch.	Root	Jihwang	25	-	-	-
Scrophularia buergeriana Miq.	Root	Hyunsam	2	-	-	-
Solanaceae						
Lycium chinense Mill.	Cortex	Jigolpi	3	-	-	21.8
Umbelliferae						
Angelica gigas Nakai	Root	Dangguey	12	-	12.57±6.80	77.9
Bupleurum falcatum L.	Root	Sihyo	4	-	-	62.7
Cnidium officinale Makino	Rhizome	Cheongoong	2	86.38±4.71	113.00±5.86	-
Ledebouriella seseloides (Hoffm.) Wolff	Root	Bangpoong	2	-	-	-
Ostericum koreana Kitagawa	Root	Ganghwal	2	-	-	-
Zingiberaceae						
Amomum cardamomum L.	Fruit	Baeckdoogoo	1	-	-	-
Amomum tsao-ko Crevost et Lemarie	Fruit	Chogwa	1	-	-	65.4
Amomum villosum Lour.	Fruit	Sain	1	-	-	81.2
Rosiglitazone (10 μM)				167.46±8.70		ND
Control				0.0±2.59		0.0±0.23

ND: Not determined, -: Inactive.

traditional prescriptions and 89 kinds of herbs in those prescriptions. These traditional medicine herbs were used in present.

Herb materials and preparation

We had investigated 71 herb plants, except for medicines that are not currently used in 89 herbs. These 71 herb plants were supplied from Semyung University Oriental Hospital in Korea. Semyung University Oriental Hospital has a clinical trial center and can study clinical trial study. Also Semyung University Oriental Hospital has treated diabetes mellitus patients and other disease by Korea oriental disease.

Preparation of plant extracts

Dried herbs were purchased and Oriental medicine doctors used the dried herbs. Herb plants part extracted for each species are shown in Table 2. Herb plants were extracted with 50% EtOH for 24 hours at room temperature, after they were concentrated under reduced pressure. Samples were freeze-dried and dissolved in dimethylsulfoxide (DMSO). The final sample concentration in DMSO was 10 mg/ml. Samples were kept in freezer at -20°C.

PPAR-γ agonist test

3T3-L1 (mouse fibroblast) cell line was obtained from American Type Culture Collection (ATCC, USA). 3T3-L1 cell was grown in Dulbecco's modified eagle's medium (Gibco, USA) supplement with 10% (v/v) calf serum (Invitrogen, USA) in a humidified incubator at 37°C and 5% CO_2. 3T3-L1 cells were seeded into 96-well plates (Nunc, USA) under the

growth conditions described above (1×10^4 cells/well). To induce differentiation, 2-day post confluent 3T3-L1 cells (designated day 0) were fed DMEM containing 10% fetal bovine serum (Gibco, USA), 1 μM dexamethasone (Sigma, USA), and 0.5 mM 3-isobutyl-1-methylxanthine (Sigma, USA) until day 2. Cells then were fed DMEM supplemented with 10% FBS for 2day, after which they were fed every other day with DMEM containing 10% FBS. Extract was dissolved in DMSO (Sigma, USA) and was added to the PBS at indicated concentration. The cells were harvested 8 days after the initiation of differentiation for AdipoRed staining an indicator of cell differentiation rate. The cells were washed with phosphate buffered saline (PBS, pH 7.2) twice, fixed with 4% formaldehyde (Sigma, USA) at room temperature for 5h, and stained with AdipoRed assay reagent (Lonza, USA) for 10 min. After 10 minutes, they were placed on the plate in the fluorometer (Perkin elmer, USA) and the fluorescence with excitation at 485 nm and emission 535 nm was measured. PPAR-γ agonist activity (%) was calculated using the following formula:

$$\text{PPAR-}\gamma\text{ agonist activity (\%)} = (\text{Fluorescence}_{\text{test sample}} - \text{fluorescence}_{\text{control}}) / \text{fluorescence}_{\text{control}} \times 100$$

Rosiglitazone (10 μM: Alexis Biochemicals, Hornby, ON), a PPAR-γ agonist of the thiazolidinedione family, was used as a positive control, while vehicle in proliferation medium was used as a negative control.

α-glucosidase inhibition assay

Samples (10μl) were added to a 96-well containing 0.1 M sodium phosphate buffer (pH 6.8, 84 μl) and 50 mM para-nitrophenyl glucopyranoside (5 μl), 5U α-glucosidase (1 μl), then incubated for 20 minutes at 37°C. The reaction was stopped by addition 200 μl of 2M NaOH and then, placed on the plate in the ELISA reader (Moledular Devices, USA). The optic density (OD) of the well at 405 nm was measured and the inhibition rate was calculated using following formula:

$$\text{Inhibition rate (\%)} = (OD_{control}-OD_{test\ sample}) / OD_{control} \times 100$$

Results and Discussion

Many herb medicines have been used in the treatment of diabetes in Korea. Herb medicines have in general not associated with marked toxic or side effects. But the action mechanism of natural medicines is not clarified. Although some herbal medicines have been reported to inhibit α-glucosidase activity, most of the experiments have been limited to *in vitro* studies or chemical-induced diabetic animal models only (Li *et al*., 2005). Also PPAR-γ agonist tests have been used to anti-diabetic effects of some herbal medicines. But these PPAR-γ agonist tests induced the complete differentiation of 3T3-L1.

In this study, we screened herb medicines for PPAR-γ agonist activity like TZDs (rosiglitazone). The TZD classes of insulin-sensitizing compounds such as rosiglitazone and pioglitazone, which lower hyperglycemia, are PPAR-γ agonists (Staels and Fruchart, 2005). However, the limitations and the side-effects of these drugs have driven researchers to look for a new type of drug that could be of benefit for the treatment of some of these metabolic disorders. We used MD media (isobutyl-methylxanthine dexamethasone) to differentiate pre-adipocyte and total 16 herb plants had a PPAR-γ agonist activity (Table 2). Specially, *Alisma orientale* Juz. (108.41%), *Ephedra sinica* (98.22%), *Sasa japonica* Makino var. *purpurascens* Nakai (140.68%), *Astragalus membranaceus* Bunge (106.79%), *Cnidium officinale* Makino (113.00%) showed high PPAR-γ agonist activity rates compared with rosiglitazone's (167.46%).

α-Glucosidase is one of a number of glucosidase located in the brush-border surface membrane of intestinal cells, and is a key enzyme of carbohydrate digestion (Caspary, 1978). α-Glucosidase inhibitors block the actions of α-glucosidase enzymes in the small intestine, which is rate-limiting in the conversion of oligosaccharides and disaccharides to monosaccharides, necessary for gastrointestinal absorption. Postprandial glucose peaks may be attenuated by delayed glucose absorption. The main benefits attributable to α-glucosidase inhibitors are reductions in both postprandial glycemic levels and in the total range of postprandial glucose levels (Chiasson *et al*., 1994; Lebovitz, 1998). However, it is well documented that synthetic α-glucosidase inhibitors have undesirable side effects, such as flatulence, diarrhea and abdominal cramping. In addition,

some of them may increase the incidence of renal tumors and serious hepatic injury and acute hepatitis (Charpentier *et al*., 2000; Moller, 2001).

In this α-glucosidase inhibition assay, 36 herbs had α -glucosidase inhibition (Table 2). Specially, *Cornus officinalis* S. et Z. (90.3%), *Cinnamomum cassia* Blume (89.2%), *Psoralea corylifolia* L. (89.8%), *Paeonia japonica* (Makino) Miyabe (92.4%), *Paeonia suffruticosa* Andr (93.2%), showed high α -glucosidase inhibition rates.

In this study, we found out the anti-diabetic effect of herb medicine in Korean traditional medicine by PPAR-γ agonist test and α-glucosidase inhibition assay. Our results of this study provide insight into effects and action mechanism of these herbs, a traditional Korea medicine for diabetes.

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