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Review

Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus

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Abstract

The rapidly increasing diabetes mellitus is becoming a serious threat to mankind health in all parts of the world. The control and treatment of diabetes and its complications mainly depend on the chemical or biochemical agents, but the fact is that it has never been reported that someone had recovered totally from diabetes. With the distinctive traditional medical opinions and natural medicines mainly originated in herbs, the traditional Chinese medicine performed a good clinical practice and is showing a bright future in the therapy of diabetes mellitus and its complications. Based on a large number of chemical and pharmacological research work, numerous bioactive compounds have been found in Chinese medicinal plants for diabetes. The present paper reviews 86 natural medicines with regards to their origin, anti-diabetic active principles and/or pharmacological test results, which are commonly used in the traditional Chinese medical system and have demonstrated experimental or/and clinical anti-diabetic effectiveness. Among these natural medicines, 82 originate from plants and 4 from animals or insects, which covers 45 families. It is strongly significant to pay close attention to traditional Chinese medical therapeutics and natural medicines for treatment of diabetes mellitus and its complications.

Keywords: Diabetes mellitus; Traditional Chinese medicine; Natural medicines; Medicinal plants; Review

1. 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. There are two types of diabetes, namely type 1 and type 2. Type 1, insulin-dependent diabetes mellitus (IDDM), in which the body does not produce any insulin, most often occurs in children and young adults. People with type 1 diabetes must take daily insulin injections to stay alive. Type 1 diabetes accounts for 5–10% of diabetes. Type 2, noninsulin-dependent diabetes mellitus (NIDDM), in which the body does not produce enough, or properly use, insulin, is the most common form of the disease, accounting for 90–95% of diabetes. Type 2 diabetes is nearing epidemic proportions, due to an increased number of elderly people, and a greater prevalence of obesity and sedentary lifestyles. As a very common chronic disease, diabetes is becoming the third "killer" of the health of mankind along with cancer, cardiovascular and cerebrovascular diseases because of its high prevalence, morbidity and mortality.

The cause of diabetes is a mystery, although both genetic and environmental factors such as obesity and lack of exercise appear to play a role. Ethnic and racial differences have been found in heterogeneous populations within the same area. As a rule, incidence is highest in Scandinavian countries, intermediate in the US, Spain, and Israel, and lowest in Asian and most Latin American countries. Most researchers believe that, in the presence of a genetic predisposition, something in the environment triggers the development of diabetes.

With a long course and serious complications often resulting in high death-rate, the treatment of diabetes spent vast amounts of resources including medicines, diets, physical training and so on in all countries. To the people who have suffered from diabetes, medicinal therapy is the unique alternative. Up to now, many kinds of anti-diabetic medicines

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have been developed for patients, but almost all are chemical or biochemical agents. The fact is that it has never been reported that someone had recovered totally from diabetes. The traditional Chinese medicine demonstrated a good practice and shows a bright future in the therapy of diabetes and its complications because of distinctive traditional medical theory and Chinese medicines. Therefore, it is significant to understand the Chinese traditional therapeutics and the natural medicines from traditional medicinal plants for diabetes. In this respect, the rich Chinese traditional medicines with available large numbers of medicinal plants offer a great potential for such discovery.

2. Mechanism and present drugs for therapy of diabetes mellitus

The present treatment of diabetes is focused on controlling and lowering blood glucose to a normal level. The mechanisms of both western medicines and the Chinese traditional medicines to lower blood glucose are:

- to stimulate β-cell of pancreatic islet to release insulin;
- to resist the hormones which rise blood glucose;
- to increase the number or rise the appetency and sensitivity of insulin receptor site to insulin;
- to decrease the leading-out of glycogen;
- to enhance the use of glucose in the tissue and organ;
- to clear away free radicals, resist lipid peroxidation and correct the metabolic disorder of lipid and protein;
- to improve microcirculation in the body.

Based on the above-mentioned mechanisms, the drugs clinically used to treat diabetes can be mainly divided into insulin, insulin-secretagogues, insulin sensitivity improvement factor, insulin-like growth factor, aldose reductase inhibitor, α-glucosidase inhibitors and protein glycation inhibitor, almost all of which are chemical and biochemical drugs (Liu and Wang, 1996; Zhao, 1999). The effect of these drugs is only aimed to lower the level of blood glucose. Moreover, in most cases, side-effect such as hypoglycemia, lactic acid intoxication and gastrointestinal upset appear after patients took these medicines.

The drugs commonly used in clinic to treat or control diabetes are the following:

Insulin:	There are many kinds of preparations
Sulfonylureas (*SU*):	Tolbutamide (D_{860}, Orinase), Glibenclamide (Glyburide, HB419, Micronase, Daonil), Gliclazide (Diamicron), Glibenese (Minidiab), Glurenorm (Gliquidone), Glutril (Glibornuride) and Glimepiride, and so on
Biguanide (*BG*):	Phenformin (Phenethyldiguanidi Hydrochloridum, Diabenide, DBI), Dimethylbiguanide (FluamineMetformin, Diaformin, Diabex, Mellitin, Obin, Melbine, Metformin, Hydrochloride, Glucophage, DMBG)
α-Glucosidase inhibitors (*α-GDI*):	Glucobay (Acarbose), Voglibose, Miglitol, Emiglitate, Glyset, Precose
Aldose reductase inhibitor (*ARI*):	Tolrestat, Alredase, Epslstat, Kinedak, Imirestat, Opolrestat
Thiazolidinediones (*TZD*):	Troglitazone, Rosigitazone, Pioglitazone, Englitazone
Carbamoylmethyl benzoic acid (*CMBA*):	Repaglinide
Insulin-like growth factor (*IGF*):	IGF-1
Others:	Dichloroacetic acid

3. Traditional Chinese medical opinion about the therapy of diabetes

With thousands year of medical practice, a great deal of valuable experience has been accumulated in the traditional Chinese medical system for diabetes therapy.

In the traditional Chinese medical system, according to its clinical manifestations, diabetes mellitus is categorized as *Xiaokezheng* or *xiaodanzheng*, both of which mean diabetes. It is attributed to *yin*-deficiency diathesis, improper diet, emotional disorders, overstrain and excessive sexual activities. The main pathogenesis lies in consumption of *yin* fluid leading to endogenous dryness-heat in the body, with *yin* deficiency as the principal aspect and dryness-heat as the secondary aspect, and often with the presence of blood stasis and phlegm retention. If prolonged *yin* deficiency impairs *yang*, this will result in deficiency of both *yin* and *yang* as well as deficiency of both *qi* and *yin*.

Chinese doctors prescribe that diabetes would rather be treated through integrated care than only by lowering blood glucose (Zhu, 1982; Liu and Tang, 2000). The syndrome differentiation of the disease should aim at the predominance of *yin* deficiency or drynessheat. Generally at the onset, *yin* deficiency predominates. As the disease progresses, there appears the coexistence of *yin* deficiency and dryness-heat, and *yin* deficiency predominates again at the late stage. Clinically, the disease is classified as the following syndromes: fluid consumption due to lung heat, excessive fire in the stomach, deficiency of kidney *yin*, deficiency of both *qi* and *yin*, and deficiency of both *yin* and *yang*. The treatment is based on the principle of eliminating heat by nourishing *yin*, moistening dryness and promoting fluid production. According to the condition of the principal and secondary aspects, deficiency and excess, as well as the location of pathological changes of the disease, the following methods are respectively adopted: clearing heat and purging fire, resolving phlegm to activate meridians, promoting blood circulation to remove blood stasis, removing dampness, nourishing the kidney to replenish *yin*, invigorating the spleen to tonify *qi*, replenishing both *yin* and *yang*, etc. Based on such a medical opinion, a general therapeutical rule is to promote blood circulation to remove blood stasis, and secondly to activate

vital energy circulation, to clear away heat in the body, to invigorate liver and kidney to activate *yang*, and to invigorate the spleen and stomach to strengthen the body (Dai, 2000; Xu and Lu, 2000).

According to the above-mentioned rule, Chinese doctors have put forward many prescriptions (mostly Compound Recipes (prescription with over two medicines)) and have applied them to the therapy of diabetes with different medical emphasis subjecting to varied symptoms of diabetics. Some classical prescriptions and folk secret recipes with outstanding curative effect have been used for hundreds of years, and are still in present use. Some of which have been developed into preparations for therapy of diabetes following the progress of modern medical and medicinal technology, and performed well, giving good effects.

Traditional Chinese medical theory plays emphasis on integrated care of body, and then remove symptoms. Compound recipes are often used by Chinese doctors for diabetes treatment based on the fact that every herb in compound recipes can provide its special function, and lastly, form an integrated function for treatment of diabetes and complications. Single herb contains multi-ingredients, but these ingredients cannot play such a role as herbs in compound recipes. Most of western medicines, which are often made of a single chemical compound, are very effective for directly relief of symptoms, such as lowering blood sugar. So, in the Chinese medical system, it is considered that the efficacy of almost all western medicines to lower blood glucose is better than Chinese traditional medicines but not good for diabetic complications. Chinese medicines are more effective not only to treat and prevent diabetic complications but also at the meantime to lower blood glucose level. Therefore, Chinese doctors often make a combination of traditional medicine with western medicine, western medicine for reducing blood sugar, traditional medicine for integrated care of body (Cheng et al., 1998).

4. Natural medicines used in the traditional Chinese medical system for diabetes therapy

In the Chinese traditional medical treatment of diabetes, Compound Recipes are often used more than Simple Recipes (prescription with one medicine) due to consideration of integrated effects of different medicines. There are hundreds of prescriptions to aim directly at different symptoms of diabetes, and about 100 of natural medicines and preparations are used in these prescriptions or folk Simple Recipes and diets for diabetes care in China, most of which come from plants. A large number of research work on these medicines and their chemical constituents, experimental and clinical anti-diabetic activity have been conducted yet. These natural medicines and the research results about them are compiled here.

4.1. Medicines most frequently used in anti-diabetic compound recipes

The investigation shows that there are about 33 of the Chinese traditional medicines most frequently used in Chinese traditional prescriptions for the clinical treatment of diabetes and its complications.

4.1.1. Radix Astragali seu Hedysari

The roots of *Astragalus membranaceus* (Fisch.) Bunge var. *mongholicus* (Bunge) Hsiao and *Astragalus membranaceus* (Fisch.) Bunge, family *Leguminosae*. This medicine almost appears in every anti-diabetic Compound Recipe. The traditional Chinese medicine thinks that action of Radix Astragali seu Hedysari is to invigorate vital energy and spleen to activate *yang*. Astragalus polysaccharides have an effect to two-dimensionally regulate the level of blood glucose, which can increase the blood glucose of hypoglycemic animals or humans to normal level, and significantly lower the level of blood glucose, triglyceride and myocardial calcium, improve the abnormalities of myocardial ultrastructure and the metabolism of diabetic rats and mice (Ye et al., 2000; Zhang et al., 2001), and inhibit the onset of type 1 diabetes in nonobese diabetic mice (Chen et al., 2001). *Astragalus membranaceus* was reported to have an effect for diabetic complications, such as protecting the myocardium in diabetic nephropathy by inhibiting lipid peroxidation (Chen et al., 2001), prolonging the incubation period of late diabetic neuropathy by decreasing the motion nerve conduction velocity as an aldose reductase inhibitor (Gao et al., 1998), and exerting a beneficial effect on experimental diabetic nephropathy by suppressing the renal hypertrophy and microalbuminuria (Xu et al., 1997).

4.1.2. Radix Rehmanniae and Radix Rehmanniae Praeparata

Radix Rehmanniae is the roots of *Rehmannia glutinosa* Libosch., family *Scrophulariaceae*; Radix Rehmanniae Praeparata is also the roots of *Rehmannia glutinosa*, prepared by steaming it with wine and drying repeatedly. The pectin-like polysaccharide, obtained from the rhizome of *Rehmannia glutinosa* Libosch. f. *hueichingensis* Hsiao, exhibited hypoglycemic activity in normal and streptozotocin diabetic mice. The mechanism of the hypoglycemic activity is to stimulate the secretion of insulin and reduce the glycogen content in the liver of normal mice (Kiho et al., 1992; Zhang et al., 1996). Some preparations of this plant, for example, Seishin-kanro-to (Miura et al., 1997) and Shokatsu-cha (Xiao-Ke-Ca) (Sanae et al., 1996), have been developed and clinically used for the treatment of diabetics. Besides polysaccharides, iridoids (Nishimura et al., 1990a,b), iridoid glycosides rehmannioside A, B, C, and D (Oshio and Inouye, 1982), phenethyl alcohol derivatives leucosceptoside A, purpureaside C (Nishimura et al., 1990a,b) and monocyclic sesquiterpenes and their glycosides (Nishimura et al., 1991) were isolated from the

roots of *Rehmannia glutinosa* as the active ingredients for treatment of diabetic complications.

4.1.3. Radix Trichosanthis

The roots of *Trichosanthes kirilowii* Maxim., family *Cucurbitaceae*. This medicine has a long history used in prescriptions for diabetes therapy in China. Bioactivity-guided fractionation obtained five glycans termed as trichosans A, B, C, D and E, showing an anti-hypoglycemic effect to normal mice. The main glycan, trichosan A, also exhibited activity in alloxan-induced hyperglycemic mice (Hikino et al., 1989).

4.1.4. Radix Puerariae

The roots of *Pueraria lobata* (Willd.) Ohwi., family *Leguminosae*. The active components of *Pueraria lobata* for anti-diabetes are flavonoids. One of *Pueraria lobat* flavonoids, kakonein, was experimentally identified to be effective to lower the blood glucose level of alloxan or adrenalin-induced diabetic mice (Shen and Xie, 1985). 7-(6-*O*-Malonyl-β-D-glucopyranosyloxy)-3-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one is the another constituent proved to be useful for treatment of diabetes complications such as cataract, retinopathy, neuropathy, and kidney disorders (Hirakura et al., 1989). Pueraria flavonoid (PF) is a useful preparation for patients with diabetes complicated by hyperlipidemia (Sun et al., 2002). Tectorigenin and kaikasaponin III, isolated from the flowers of *Pueraria thunbergiana* (same genus as *Pueraria lobata*), showed potent hypoglycemic and hypolipidemic effects in the streptozotocin-induced diabetic rats. The antioxidant action of tectorigenin and kaikasaponin III may alleviate the streptozotocin-induced toxicity and contribute hypoglycemic and hypolipidemic effects (Lee et al., 2000a,b). There is experimental result to show that glycosylation of human serum albumin (HSA) and rat lens protein were effectively inhibited by the ethanol extract of Radix Puerariae, which indicated that the extract can be used in treating diabetic complications (Duan et al., 2000).

4.1.5. Radix Ginseng

The roots and rhizomes of *Panax ginseng* C.A. Mey., family *Araliaceae*. Ginseng is well known to be a good tonic for health care. With two-dimensional regulation to blood glucose (to lower hyperglycemia and rise hypoglycemia, not to influence normal blood glucose), many active constituents have been isolated and some preparations of ginseng have been developed and used in clinical treatment of diabetes in China. Ginseng may be most reported among medicinal plants concerning its anti-hyperglycemic effect, active principles and mechanisms of action. The extracts of all parts of ginseng (the roots, stems, leaves and fruits) are of anti-hyperglycemic effect (Lei and Wang, 1957; Wang et al., 1990; Yang, 1991; Fang et al., 1998; Chung et al., 2001; Xie et al., 2002; Attele et al., 2002). Saponins are one of the active principles (Bao, 1981; Lee et al., 1997; Jang et al., 2001), while some saponins such as ginsenoside Rb1, Rg1 (Yamasaki, 1995; Lee et al., 1997, 1998), Re (Attele et al., 2002), Rg3 (Yamasaki, 1995), CEG, Rb2, CY (Kitamura et al., 1997), DPG-3-2 (Ng and Yeung, 1985) were isolated and experimentally or clinically confirmed to be bioactive for anti-diabetes or/and anti-diabetic complications. The mechanism of action of these saponins is to regulate the activity of enzymes related to glucose metabolism directly and/or indirectly (Lee et al., 1997, 1998), inhibit the renal disorder (Kitamura et al., 1997), promote insulin secretion (Ng and Yeung, 1985), etc. Panaxans A and B (Suzuki and Hikino, 1989a,b), I, J, K, L (Oshima et al., 1985), Q, R, S, T and U (Konno et al., 1985a,b,c,d,e) were also obtained from Radix Ginseng for anti-diabetes. The mechanism to lower blood glucose is to enhance insulin sensitivity, regulate the activity of enzymes related to glucose metabolism directly and/or indirectly (Suzuki and Hikino, 1989a,b). The ginseng polypeptides were also reported to have an anti-hyperglycemic effect (Wang et al., 1991).

4.1.6. Radix Panacis Quinquefolii

The roots and rhizomes of *Panax quinquefolium* L., family *Araliaceae*. American Ginseng (*Panax quinquefolium*) has the same tonic action as ginseng. It is often used in Compound Recipes for therapy of diabetes and complications instead of ginseng. The polysaccharides quinquefolans A, B, and C were isolated from this plant, which displayed marked anti-hypoglycemic effect in normal and alloxan-induced hyperglycemic mice (Oshima et al., 1987).

4.1.7. Rhizoma Polygonati

The rhizomes of *Polygonatum sibiricum* Red., *Polygonatum cyrtonema* Hua or the other species of the same genus, family *Liliaceae*. The methanol extract of the rhizomes of both *Polygonatum sibricum* and *Polygonatum officinale* significantly reduced the blood glucose levels of normal, streptozotocin and epinephrine-induced hyperglycemic mice (Kato and Miura, 1993, 1994). The *n*-butanol fraction of the methanol extract of *Polygonatum officinale* elicited a significant decrease in the blood glucose level of streptozotocin-induced diabetic mice (Kato and Miura, 1994). One of the active components was identified as a spirostanol glycoside PO-2 (Kato and Miura, 1993). *Polygonatum sibricum* and *Polygonatum officinale* performed anti-diabetic action by a different mechanism (Miura and Kato, 1995; Miura et al., 1995).

4.1.8. Rhizoma Polygonati Odorati

The rhizoms of *Polygonatum odoratum* (Mill.) Druce., family *Liliaceae*. With a long history, the medicine was often used in Chinese traditional prescriptions to treat *Xiaokezheng* (diabetes). Administration of the *n*-butanol fraction of *Polygonatum odoratum* with selenium supplementation reduced the blood glucose level and peroxidative tissue damage in streptozotocin-induced diabetic rats (Lim and Park, 2000). The anti-hyperglycemic action of Rhizoma

Polygonati Odorati was also reported by Jia (1991). The active principles to lower blood glucose level may be saponins.

4.1.9. Fructus Coini

The pulps of *Cornus officinalis* Sieb. et Zucc., family *Cornaceae*. Fructus Coini is a traditional tonic with actions to invigorate the liver and kidney, astringe and preserve essence. The extract of Corni Fructus has potent anti-diabetic activity towards streptozotocin-induced diabetic rats. Ursolic acid and oleanolic acid found in the extract were responsible for the activity (Yamahara et al., 1981). Based on decreasing postprandial plasma glucose and insulin level of noninsulin-dependent diabetic rats, further research was carried out. The results indicated that the alcohol extract of *Cornus officinalis* could increase GLUT4 mRNA and its protein expression in NIDDM rats by promoting proliferation of pancreatic islets and increasing postprandial secretion of insulin and therefore accelerate glucose transport (Qian et al., 2001).

4.1.10. Hirudo

The whole body of *Whitmania pigra* Whitman, and several species of the same family *Hirudinidae*. *Whitmania pigra* is one of the traditional Chinese drugs commonly used in clinical practice for promoting blood circulation and relieving stasis. The extracts using different extracting methods showed different anticoagulant and anti-thrombotic activity (Ding et al., 1994). An active peptide, called leech excitatory peptide, has been isolated (Nagahama et al., 1999).

4.1.11. Rhizoma Coptidis

The rhizomes of *Coptis chinensis* Franch. and *Coptis deltoidea* C.Y. Cheng et Hsiao, family *Ranunculaceae*. The water extract of *Coptis chinensis* Franch. can decrease serum glucose level in normal mice. Berberine, the major component of the plant, had an anti-hypoglycemic effect in normal, alloxan-induced, and spontaneous diabetic KK mice. Berberine also antagonized the hyperglycemic effect induced by i.p. glucose or adrenaline in normal mice, decreased serum cholesterol level of mice fed a high-cholesterol diet, and inhibited the aggregation of rabbit platelet in vitro (Chen and Xie, 1986). The active character of berberine is similar to both sulfonylureas and biguanide.

4.1.12. Fructus Lycii and Cortex Lycii Radicis

The fruits and root cortex of *Lycium barbarum* L., family *Solanaceae*. The experimental results from Bo and Qi (1993) showed that Cortex Lycii Radicis had an effect to lower blood glucose. Some Lycium Barbarum Polysaccharides (LBP) were obtained from the fruits of *Lycium barbarum* and observed for anti-hyperglycemic effect, of which, LBP-D demonstrated cytoprotective effect on β-cells of pancreatic islets in mice and an immune modulation therapeutic effect on diabetes (Wang et al., 1999), while LBP-X remarkably reduced blood glucose in alloxan-induced diabetic rabbits (Luo et al., 1997).

4.1.13. Poria

The sclerotium of *Poria cocos* (Schw.) Wolf., family *Polyporaceae*. The triterpene dehydrotrametenolic acid was isolated from dried sclerotia of *Poria cocos*, and demonstrated to have an anti-hyperglycemic effect in a mouse model of noninsulin-dependent diabetes mellitus as an insulin sensitizer (Sato et al., 2002). This natural product is a promising candidate for a new type of insulin-sensitizing drug.

4.1.14. Rhizoma Atractylodis

The rhizomes of *Atractylodes lancea* (Thunb.) DC. or *Atractylodes chinensis* (DC.) Koidz. and *Atractylodes japonica* Kiodz., family *Compositae*. Active constituents for anti-hyperglycemia are atractans A, B, C (Konno et al., 1985a,b,c,d,e). β-Eudesmol, a sesquiterpenoid alcohol isolated from *Atractylodes lancea*, can potentiate succinylcholine-induced neuromuscular blockade, while the potentiating effect is greater in diabetic muscles than in normal ones (Kimura et al., 1995).

4.1.15. Rhizoma Anemarrhenae

The rhizomes of *Anemarrhena asphodeloides* Bunge., family *Liliaceae*. The water extract of the rhizoma (90 mg/kg) reduced the blood glucose level after oral administration and also tended to reduce serum insulin levels in KK-Ay mice. The active components were confirmed to be mangiferin and its glucoside (mangiferin-7-*O*-β-D-glucoside) (Miura et al., 2001a,b; Ichiki et al., 2001). It was inferred that mangiferin and its glucosides exert an anti-diabetic activity by increasing insulin sensitivity (Ichiki et al., 1998; Miura et al., 2001a,b). Polysaccharides were also extracted from the root and stem of *Atractylodes asphodeloides*, and showed a significant decrease of the blood glucose and liver glycogen in mice at doses of 50, 100, and 300 mg/kg (Wang et al., 1996). Polysaccharides anemarn A, B, C and D were further isolated as active constituents, of which, anemarn B was the best one (Takahashi et al., 1985a,b). Hypoglycemic activity-guided fractionation also resulted in isolation of a new steroid glycoside, pseudoprototimosaponin AIII (Nakashima et al., 1993).

4.1.16. Radix Ophiopogonis

The root tubers of *Ophiopogon japocicus* (Thunb.) Ker-Gawl., family *Liliaceae*. Polysaccharides isolated from Radix Ophropogonis significantly lowered blood sugar of normal and alloxan-diabetic mice (Zhang and Wang, 1993a,b). The complex prescription of Ginseng and *Ophiopogon japonicus* significantly reduced blood sugar in alloxan-induced diabetic mice, but had no distinct effect in normal mice (Fang et al., 1998).

4.1.17. Fructus Ligustri Lucidi

The fruits of *Ligustrum lucidum* Ait., family *Oleaceae*. The research result of Hao et al. (1992) indicated that Fructus

Ligustri Lucidi was effective to lower blood glucose level to normal and diabetic mice. It was inferred that oleanolic acid is the active constituent.

4.1.18. *Fructus Mori, Folium Mori and Cortex Mori Radicis*

The fruits, leaves and root epidermis of *Morus alba* L., family *Moraceae*. Moran A, a polysaccharide, has been isolated and proved to have a marked effect to lower the blood glucose of normal and alloxan-diabetic mice at a low dose (Hikino et al., 1985a,b). Ethyl acetate- and *n*-butanol-fractions of the leaves of *Morus insignis* showed a significant anti-hypoglycemic activity on streptozotocin-induced hyperglycemic rats. From these anti-hypoglycemic activity-showing fractions, two new compounds, mulberrofuran U and moracin M-3-*O*-β-D-glucopyranoside were obtained, along with six known compounds, i.e. β-sitosterol, β-sitosterol-3-*O*-β-glucopyranoside, moracin M, kaempferol-3-*O*-β-glucopyranoside, ursolic acid and quercetin-3-*O*-β-glucopyranoside (Basnet et al., 1993).

4.1.19. *Fructus Schisandrae*

The fruits of *Schisandra chinensis* (Turcz.) Baill. and *Schisandra sphenanthera* Rehd. et Wils., family *Mognoliaceae*. This is a common Chinese medicine used to invigorate kidney to activate *yang*. Lignans are effective as aldose reductase inhibitors, which are useful in treating diabetes-related diseases (Iketani et al., 1989).

4.1.20. *Gynostemmae Herba*

The stems and leaves of *Gynostemma pentaphyllum* (Thunb.) Mak., family *Cucurbitaceae*. It is sometimes called as “southern ginseng” in China because of the similarity of active compounds and actions to ginseng. Saponins were inferred to be the active compounds which are identical to ginseng. Crude saponin fractions isolated from Gynostemmae Herba significantly decreased the plasma glucose level and increased plasmas triglyceride level to diabetic rats at a dose of 1 mg/kg, compared with glibenclamide-treated or normal rats (Jang et al., 2001).

4.1.21. *Radix Salviae Miltiorrhizae*

The roots and rhizomes of *Salvia miltiorrhiza* Bunge., family *Labiatae*. Radix Salviae Miltiorrhizae is an important Chinese medicine to promote blood circulation to remove blood stasis in traditional Chinese medical system. It is often used in Compound Recipes for therapy of diabetic complications. A USA patent showed the aqueous extract of Salviae Miltiorrhizae Radix has been administered to diabetic patients for care of diabetic nephropathy (Li et al., 2000). Considering the fact that Salvia Miltiorrhiza Composita (SMCo) significantly increased the SOD levels, it is inferred that SMCo could resist lipid peroxidation injury and be helpful for diabetic complications (Jiang et al., 1997).

4.1.22. *Rhizoma Phragmitis*

The fresh or dried rhizomes of *Phragmites communis* Trin., family *Gramineae*. It is used in diabetic prescriptions for diabetic complications because of the actions to clear away heat and promote the production of fluid.

4.1.23. *Rhizoma Alismatis*

The stem tubers of *Alisma orientale* (Sam.) Juzep., family *Alsmataceae*. It is used in prescriptions for diabetic complications because of the actions to promote diuresis to eliminate dampness from the lower-*jiao* and expel heat.

4.1.24. *Semen Cuscutae*

The seeds of *Cuscuta chinensis* Lam., family *Convolvulaceae*. It is used in prescriptions for diabetic complications because of the actions to invigorate the kidney and supplement essence.

4.1.25. *Herba Epimedii*

The branches and leaves of *Epimedium sagittatum* (Sieb. et Zucc.) Maxim. or *Epimedium brevicornum* Maxim., family *Berberidaceae*. It is used in prescriptions for diabetic complications because of the actions to invigorate the kidney and strengthen *yang*.

4.1.26. *Radix Clematidis*

The roots and rhizomes of *Clematis chinensis* Osbeck and other species of the same genus, family *Ranunculaceae*. It is used in prescriptions for diabetic complications because of the actions to expel wind and dampness, and dredge the channel.

4.1.27. *Radix Notoginseng*

The roots of *Panax notoginseng* (Burk.) F. H. Chen, family *Araliaceae*. Radix Notoginseng is a famous Chinese medicine used for injury from fall injury because of the action to promote blood circulation to remove blood stasis in the traditional Chinese medical system. It has the action to two-dimensionally regulate blood glucose. Sanchinoside C1 (ginsenoside Rg1), one of the major effective components of *Panax notoginseng*, could lower plasma glucose level in alloxan-diabetic mice, and synergizing the action of insulin in normal animals (Gong et al., 1991). It was reported that the extract of *Panax notoginseng* was administrated to patients with diabetic nephropathy, and showed to be beneficial to resume the balance of *T*/*K* and improve microcirculation, reduce whole blood viscosity and decrease urinary albumin so as to retard the progress of diabetic nephropathy (Lang et al., 1998).

4.1.28. *Herba Dendrobii*

The stems of *Dendrobium nobile* Lindl., *Dendrobium chrysanthum* Wall. ex Lindl., *Dendrobium loddigesii Rolfe* and *Ephemerantha fimbriata* (Bl.) Hunt et Summerh, family *Orchidaceae*. The action of Herba Dendrobii is to nourish *yin*, clear heat, benefit stomach and promote the production

of body fluid (Ou, 1992). This medicine was reported to have anti-hyperglycemic effect (You and Wang, 2000).

4.1.29. Concha Ostreae

The shells of *Ostrea gigas* Thunberg, *Ostrea talienwhanensis* Crosse or *Ostrea rivularis* Gould., marine organisms, family *Ostreidae*. This Chinese medicine has an action to benefit *yin* and suppress the sthenic *yang*, astringe, invigorate the kidney to preserve essence. It is often used in prescriptions for diabetes treatment.

4.2. Medicines often used in anti-diabetic compound recipes

In addition, there are 22 traditional Chinese medicines often appear in the Chinese traditional prescriptions for clinical treatment of diabetes and its complications.

4.2.1. Radix Lithospermi

The roots of *Lithospermum erythrorhizon* Sieb. et Zucc., family *Boraginaceae*. Glycans lithosperman A, B, C were isolated from Radix Lithospermi and proved to be active to lower blood glucose of normal mice, of which, lithosperman C is the best one (Konno et al., 1985a,b,c,d,e). These compounds can be manufactured through cell culture of callus (Miyamoto et al., 1987).

4.2.2. Radix Aconiti and Radix Aconiti Praeparata

Radix Aconiti is the axial roots of *Aconitum carmichaeli* Debeaux., family *Ranunculaceae*, prepared by soaking in water or in saturated lime water and then boiled until the white core disappears and no numbness occurs when tasted, then sliced and dried. Radix Aconiti Praeparata is the roots of *Aconitum carmichaeli*, prepared into salty aconiti, black aconiti, white aconiti and bland aconiti using different procedures. The two medicines are often used to invigorate liver and kidney to activate *yang*, and to expel wind and dampness in the body. Aconitians A, B, C, D were isolated from *Aconitum carmichaeli* roots and showed remarkable effect to lower the blood glucose in normal and alloxan-diabetic mice (Konno et al., 1985a,b,c,d,e).

4.2.3. Radix Acanthopanacis Senticosi

The roots or rhizomes of Acanthopanax senticosus (Rupr. et Maxim.) Harms., family Araliaceae. Saponins are the active components for anti-diabetes (Sui, 1994). The doses 10 and 200 mg/kg of senticoside A were effective to lower the blood glucose of diabetic mice or rat induced by glucose, alloxan and adrenalin. Ni et al. (1998) reported that saponins possess anti-lipid peroxidation activity to protect the vascular endothelium, and prevent diabetic complications.

4.2.4. Radix Paeoniae Rubra and Radix Paeoniae Alba

The roots of *Paeonia veitchii* Lynch and *Paeonia lactiflora* Pall., family *Ranunculaceae*. The constituents of Glycyrrhizae Radix (GR) and Paeonie Radix (PR), used in Kampo medicines for the treatment of diabetic neuropathy, showed potent aldose reductase inhibitory activities. Tetra- and penta-*O*-galloyl-β-D-glucose, isolated from PR, inhibited RLAR by 77.6 and 61.0%, respectively (Aida et al., 1989). Paeoniflorin and 8-debenzoylpaeoniflorin were isolated from the dried roots of *Paeonia lactiflora* Pall., which produced a significant effect to lower blood sugar and increase glucose utilization in streptozotocin-treated rats (Hsu et al., 1997).

4.2.5. Radix et Rhizoma Rhei

The roots and rhizomes of *Rheum palmatum* L., *Rheum tanguticum* Maxim. ex Balf. or *Rheum officinale* Baill., family *Polygonaceae*. Radix et Rhizoma Rhei showed a good effect when used in clinical treatment of diabetic nephropathy (Zhao, 1996). Polysaccharides may be the active constituents for the treatment of diabetes and complications.

4.2.6. Rhizoma Pinelliae

The Rhizomes of *Pinellia ternata* (Thunb.) Breit., family *Araceae*. The so-called Flavone C-glycoside was isolated from the rhizomes of *Pinellia ternate* for anti-diabetes. The dose of 100 μmol/l of flavone C-glycoside could inhibit 64.7% of aldose reductase, proving that it is suitable to treat diabetic complications (Nishimura et al., 1992a,b).

4.2.7. Radix Polygalae

The roots or root cortex of *Polygala tenuifolia* Willd. or *Polygala senega* L. and *Polygala senega* L. var. *latifolia* Torrey et Gray, family *Polygalaceae*. The anti-hypoglycemic effect of *Polygala senega* var. *latifolia* was investigated in normal and KK-Ay mice. The *n*-butanol extract of *Polygala senega* (5 mg/kg) showed a significant decrease in the glucose level of normal and KK-Ay mice, but did not produce a change in the blood glucose of streptozotocin-induced diabetic mice (Kako et al., 1996). The compounds with anti-hypoglycemic activity were isolated and identified as triterpenoid glycosides, i.e. senegins II, III, IV and desmethoxysenegin II (Kako et al., 1995, 1996, 1997).

4.2.8. Fructus Hordei Germinatus

The germinant fruits of *Hordeum vulgare* L., family *Gramineae*. It is used in anti-diabetic prescriptions for the action to strengthen the stomach and improve digestion. With hypoglycemic and hyperinsulinemic effects in NIDDM subjects, barley seems to mobilize insulin in NIDDM. This makes it a suitable cereal for diabetes mellitus (Shukla et al., 1991).

4.2.9. Cortex Phellodendri

The barks of *Phellodendron amurense* Rupr. or *Phellodendron chinensis* Schneid., family *Rutaceae*. Enhanced activity of the lipid peroxidation and oxidative damages have been implicated in the pathogenesis of diabetic kidney complications. An aqueous extract of a mixture of Phellodendron

Cortex and Aralia Cortex has an antioxidant effect by reducing lipid peroxidation and protein carbonylation as well as by elevating the ratio of GSF/GSSG in diabetic kidney (Lee et al., 2000a,b).

4.2.10. Fructus Arctii

The fruits of *Arctium lappa* L., family *Compositae*. This medicine is used in anti-diabetic prescriptions for its diuretic and laxative action. The extract of Fructus Arctii was reported to show significant anti-hyperglycemic effect in diabetic rats (Ou, 1992; You and Wang, 2000).

4.2.11. Fructus Xanthii

The fruits and involucres of *Xanthium sibiricum* Patr., family *Compositae*. Lowering blood sugar, with a similar mechanism to phenethyl biguanide (Ou, 1992; You and Wang, 2000).

4.2.12. Bombyx Batryticatus

The larva in fourth to fifth stadium of *Bombyx mori* L. (silkworm), family *Bombycidae*, infected by *Beauveria bassiana* (Bals.) Vuill. or dried silkworm chrysalis. Bombyx Batryticatus is well-known to have an anti-hyperglycemic effect in the traditional Chinese medical system. Conjugated linoleic acid (CLA) obtained from silkworm may have a biological activity for anti-diabetes (Park et al., 2001). Also, some alkaloids were reported to have the possibility of preventing the onset of diabetes and obesity (Asano et al., 2001).

4.2.13. Gecko

The bodies (removed off internal organs) of *Gekko gekko* L., family *Gekkonidae*. Gecko is used in Chinese medical prescriptions for invigorating the lung and kidney. An ethanol extract of *Gekko gekko* showed a marked anti-hyperglycemic effect to alloxan-induced diabetic mice (You and Wang, 2000).

4.2.14. Radix Stephaniae Tetradrae

The roots of *Stephania tetradra* S. Moore or *Sinomenium acutum* (Thunb.) Rehd. et Wils., family *Menispennaceae*. Animal tests indicated that an extract of *Stephania tetradra* could prevent hyperglycemia by protecting β-cells of pancreatic islet (You and Wang, 2000).

4.2.15. Rhizoma Polygoni Cuspidate

The rhizomes and roots of *Polygonum cuspidatum* Sieb. et Zucc., family *Polyconaceae*. Chen (1996), You and Wang (2000) reported that Rhizoma Polygoni Cuspidate was indigenously used as Simple Recipe to treat diabetes in China. This medicine has the action to promote blood circulation and remove blood stasis. Polydatin, isolated from Rhizoma Polygoni Cuspidate, can dilate blood capillaries, improve micro-circulation and inhibit thrombosis (Ou, 1992), which may be helpful for the treatment of diabetic complications.

4.2.16. Radix Platycodi

The roots of *Platycodon grandiflorum* (Jacq.) A. DC., family *Campanulaceae*. Dietary of *Platycodon grandiflorum* resulted in a significant decrease in the concentration of plasma triglycerides, plasma cholesterol, postprandial glucose and fasting plasma insulin levels in both lean and obese Zucker rats. Therefore, it was suggested that dietary *Platycodon grandiflorum* may be useful in prevention and improvement of metabolic disorders characterized by hyperinsulinemia states such as noninsulin-dependent diabetes mellitus, syndrome X, and coronary artery disease (Kim et al., 2000).

4.2.17. Radix Codonopsis Pilosulae

The roots of *Codonopsis pilosula* (Franch.) Nannf., and several other species of the same genus, family *Campanulaceae*. This medicine is considered as tonic to supplement middle-*jiao* energy, benefit the lung, promot the production of body fluid and nourish blood, which is identical to the therapeutical rule of diabetes.

4.2.18. Radix Scrophulariae

The roots of *Scrophularia ningpoensis* Hemsl., family *Acrophulariaceae*. A pharmacological test showed that *Scrophularia ningpoensis* did not increase nor decrease the insulin receptor binding rate, but cannot completely deny the beneficial effect of this medicine in the treatment of diabetes mellitus (Liu et al., 1991). The further research should be carried out to isolate active components and explain the anti-diabetic mechanism.

4.2.19. Rhizoma Ligustici Chuanxiong

The rhizomes of *Ligusticum chuanxiong* Hort., family *Umbelliferae*. Clinical practice showed that curative effect of Rhizoma Ligustici Chuanxiong combined with photocoagulation was better than photocoagulation alone in the treatment of diabetic retinopathy (Han and Wang, 2001).

4.2.20. Radix Angelicae Sinensis

The roots of *Angelica sinensis* (Oliv.) Diels., family *Umbelliferae*. Radix Angelicae Sinensis is a traditional medicine well known as agent to enrich blood and promote blood circulation, which is often used in anti-diabetic prescriptions for therapy of diabetic complications.

4.3. Natural products commonly used in traditional Chinese diets for the control or/and treatment of diabetes and its complications

The following 13 of the traditional Chinese medicines or natural products are commonly used in diets for the control or/and treatment of diabetes and its complications.

4.3.1. Fructus Balsampear

The fruits of *Momordica charantia* L., family *Cucurbitaceae*. *Momordica charantia* has been used as a treatment

for diabetes in India and China for thousands of years. At present, unripe fruits, seeds and aerial parts of *Momordica charantia* Linn. have a widespread use as vegetable and phytomedicine in various parts of the world to treat diabetes. Oral administration of the extract, fruit juice or seed powder of *Momordica charantia* caused a significant reduction in fasting blood glucose and improved glucose tolerance in normal and diabetic animals and in humans (Raman and Lau, 1996; Miura et al., 2001a,b; Fan and Cui, 2001; Srivastava et al., 1993; Ahmed et al., 2001; Ahmad et al., 1999), also retardate retinopathy in alloxan-induced diabetic rats (Srivastava et al., 1987). Animal and in vitro data support both the insulin secretagogue and insulinomimetic activity of the fruit (Raman and Lau, 1996). When purified compounds were administered to patients, however, the effective dosage was found to be significantly higher than the required dosage in the natural form (Riskey and Jain, 1998). A wide range of compounds have been isolated from *Momordica charantia*, of which, a polypeptide (p-insulin, was named as "plant insulin"), the sterol glucoside mixture charantin and the pyrimidine nucleoside vicine have been identified as the orally anti-diabetic principles for humans and animals (Khanna et al., 1981; Wang et al., 1991; Zhang et al., 1992; Jiang, 1996; Raman and Lau, 1996).

4.3.2. Rhizoma Dioscoreae

The rhizomes of *Dioscorea opposita* Thunb., family *Dioscoreaceae*. With a long history, Rhizoma Dioscoreae was traditionally used in prescriptions or diets to treat *Xiaokezheng* (diabetes) in China. The water decoction of *Dioscorea opposita* has an anti-hyperglycemic effect to experimental diabetic mice (Hao et al., 1991). Polysaccharides were considered to be the active constituents.

4.3.3. Stigma Maydis

The styles and stigmas of *Zea mays* L., family *Gramineae*. As folk Simple Recipe with a long history, Stigma Maydis is very effective to be used for diabetes. The anti-hyperglycemic effect of Stigma Maydis has been confirmed by pharmacological test (Li et al., 1995).

4.3.4. Semen Fagopyri Cymosi

The seeds of *Fagopyrum cymosum* (Trev.) Meisn., family *Polygonaceae*. It has a long history of use as Chinese traditional food for diabetes care. The effects of *Fagopyrum cymosum* (Trev.) Meisn. on lowering blood glucose and lipid were observed in diabetic animals and patients (Wang, 1995; Qin, 1992). A Compound Recipe including Semen Fagopyri Cymosi has been confirmed to be close or superior to glyburide on relieving symptoms, preventing obesity, decreasing blood glucose level, improving insulin-sensitivity and blood stasis (Gao and You, 2001).

4.3.5. Semen Litchi

The seeds of *Litchi chinensis* Sonn., family *Sapindaceae*. The aqueous extract of Semen Litchi (5 g/kg, i.g.) lowered the blood glucose levels in normal and alloxan-reduced diabetic mice, the hypoglycemic effect nearly equals to glibenclamide and phenformin (Kuang et al., 1997). Lychee nut has been developed into a medicinal tablet to treat diabetes, especially pregnancy diabetes in clinic in China (Shen, 1991).

4.3.6. Pericarpium Granati

The pericarpium of *Punica granatum* L., family *Punicaceae*. Pericarpium Granati is used to treat diabetes mellitus in some parts of China. Male abortive flowers of *Punica granatum* are also used for the treatment of diabetes mellitus in Unani medicine in India. Oral administration of the aqueous-ethanolic (50%, v/v) extract of *Punica granatum* flowers led to a significant blood glucose lowering effect in normal, glucose-fed and alloxan-induced diabetic rats (Jafri et al., 2000). The extract of *Punica granatum* seeds was also reported to have anti-diabetic activity (Das et al., 2001). Ursolic acid may be the active constituent.

4.3.7. Semen Coicis

The dried mature seeds of *Coix lacryma-jobi* L. var. *ma-yuen* (Roman.) Stapf., family *Gramineae*. It is a well-known healthy food for diabetes in China. Active constituents are the polysaccharides coixan A, B and C (Takahashi et al., 1986). Coixans were isolated and purified from the dried coix seeds, and showed an effect to decrease blood glucose in normal rats, while the serum insulin level increased. The anti-diabetic mechanism of coixans may be to prevent β-cells of pancreatic islet from injury induced by alloxan (Xu et al., 2000a,b; Huang et al., 1999).

4.3.8. Allii Sativi Bulbus

The bulbs of *Allium sativum* L., family *Liliaceae*. Oral administration of the ethanol extract, juice and oil of garlic remarkably lowered blood sugar in normal and alloxan-induced diabetic rats or rabbits, with an efficacy compared closely to tolbutamide (Jain and Konar, 1977; Patumraj et al., 1996; Al-Zuhair et al., 1996; Kumar and Reddy, 1999; Dong et al., 2000). The garlic extract can prevent diabetic cardiovascular complications (Patumraj et al., 1977). Allicin (diallyldisulfide-oxide) and *S*-allyl cysteine sulfoxide (the precursor of allicin and garlic oil) are the active constituents. The anti-hyperglycemic mechanism is to stimulate in vitro insulin secretion from β-cells of pancreatic islet, increase serum insulin level, improve glucose tolerance and increase liver glycogen synthesis (Mathew and Augusti, 1973; Han and Wang, 1991; Sheela and Augusti, 1992; Augusti and Sheela, 1996; Al-Zuhair et al., 1996).

4.3.9. Allii Cepa Bulbus

The bulbs of *Allium cepa* L., family *Liliaceae*. Onion, a common vegetable, has an anti-diabetic activity. Onion

feeding improved the metabolic status in diabetic conditions, probably because of hypoglycemic and hypocholesterolemic effect (Babu and Srinivasan, 1997), mediated diabetic nephropathy by lowering blood cholesterol levels and decreasing lipid peroxidation (Babu and Srinivasan, 1999). The research results about active principles showed that allyl propyldisulfide and *S*-methyl cysteine sulfoxide have an anti-diabetic and anti-hyperlipidemic effect, the latter being comparable to glibenclamide and insulin (Augusti et al., 1974; Sheela et al., 1995; Kumari et al., 1995).

4.3.10. Radix Asparragi Officinalis

The roots of *Asparrausi officinalis* L., family *Liliaceae*. The roots of *Asparrausi officinalis* are prepared into Chinese medicine used in Compound Recipes, while the fresh shoots are eaten as vegetable. This plant is well-known to be helpful for diabetes care. The active principles may be coumarins (Chen et al., 1998; Yuan et al., 1999).

4.3.11. Cordyceps

The stroma formed by *Cordyceps sinensis* (Berk.) Sacc. parasitized on the larva of *Hepialus armoricanus* Oberthru. Both the stroma and the dead larva are used medicinally. Cordyceps has been used as a tonic in the traditional medicine. The hot water extract of Cordyceps showed a mild hypoglycemic activity in alloxan or streptozotocin-induced diabetic rats by oral administration (Ji et al., 1993a,b; Kwon et al., 2001). Polysaccharide CS-F10 (Kiho et al., 1999), CS-F30 (Kiho et al., 1996) and CHWp (Ji et al., 1993a,b), obtained from cultured cordyceps, significantly lowered the plasma glucose level in normal, genetic, alloxan, streptozotocin or epinephrine-induced diabetic mice, and were confirmed as active constituents.

4.3.12. Ganoderma Lucidum seu Japonicum

The sporophore of *Ganoderma lucidum* (Leyss. ex Franch.) Karsten, family *Polyporaceae*. As both tonic nourishment and medicine, mythic fungus is helpful for care of diabetic patients. Some research results showed that polysaccharides are the active principles for anti-diabetes (Kimura et al., 1995; Zhang and Xiao, 1993). Ganoderans A and B have been isolated and confirmed to have a hypoglycemic activity (Hikino et al., 1985a,b).

4.3.13. Tremellae

The sporophore of *Tremella fusiformis* Berk., family *Tremellaceae*. Like mythic fungus, Tremellae is used in the traditional Chinese medical system as tonic nourishment and/or medicine considered helpful for diabetes care. Tremellae polysaccharides and tremellae spore polysaccharides are the active constituents (Xue et al., 1989). An acidic polysaccharide (TAP) and its degradation product (TAP-H) have been isolated and found to significantly lower level of plasma glucose, insulin, total-cholesterol and triglyceride in genetic diabetic mice (KK-Ay) (Kiho et al., 2000, 2001).

4.4. Medicinal plants with outstanding anti-diabetic potential

Some medicinal plants and their constituents (extracts and isolated compounds, etc.) in China were phytochemically and pharmacologically confirmed to have outstanding anti-diabetic activity, most of which, with a long indigenous use, often are used as Simple Recipes for diabetes therapy by folk doctors.

4.4.1. Gymnema sylvestre (Retz.) Schult (Asclepiadaceae)

This is a promising plant to be developed into a new drug for diabetes therapy. There are many reports about the action and active constituents of *Gymnema sylvestre*. After gymnemic acids I, II, III, IV, V, VI, VII and gymnemosides a, b, c, d, e, f as well as protein-bound polysaccharide components and glycosaminoglycans were isolated and administrated to diabetic animals and humans (Rathi et al., 1981; Yoshikawa et al., 1997; Sugihara et al., 2000; Tan et al., 2000), gymnemic acids III, IV, V, VII and gymnemosides b were identified as the anti-hyperglycemic active constituents. A polyol, conduritol A, may also be responsible for the cataract-suppressing effect by inhibiting lens aldose reductase (Miyatake et al., 1994). GS4, an extract from the leaves of *Gymnema sylvestre*, has an excellent effect in controlling hyperglycaemia of both types 1 and 2 diabetic patients (Baskaran et al., 1990; Miyatake et al., 1994).

4.4.2. Trigonella foenum-graecum L. (Leguminosae)

Trigonella foenum-graecum (Fenugreek) is traditionally used as food or medicine for diabetes care. The extracts, powder and gum of fenugreek seeds and leaves have been reported to have anti-diabetic and hypocholesterolemic properties in both model animals and humans (Shani et al., 1974; Ribes et al., 1986; Amin et al., 1988; Ali et al., 1995; Abdel-Barry et al., 1997; Al-Habbori and Raman, 1998; Gomez and Bhaskar, 1998; Khatir et al., 1999; Gupta et al., 2001; Vats et al., 2002). Activity has been attributed largely to fenugreek's saponins (Petit et al., 1995), high fiber content (Ali et al., 1995), the amino acid 4-hydroxyisoleucine (Sauvaire et al., 1998) and the major alkaloid trigonelline (Shani et al., 1974). Anti-hyperglycemic effect was linked to delayed gastric emptying caused by the high fiber content, inhibiting of carbohydrate digestive enzymes (Ali et al., 1995) and stimulating of insulin secretion (Sauvaire et al., 1998).

4.4.3. Prunella vulgaris L. (Labiatae)

Liu et al. (1995) reported the anti-hyperglycemic effect of the ethanol extract of *Prunella vulgaris* L. to mice. Before this report, a compound, *Jiangtangsu*, had been isolated from this plant and confirmed to have a remarkable effect to lower blood sugar levels in mice with diabetes mellitus induced by alloxan (Xu et al., 1989). The possible mechanism of *Jiangtangsu* is to repair β-cells of pancreatic islet to release insulin.

4.4.4. *Ephedra sinica Stapf., and Ephedra distachya L. (Ephedraceae)*

The glycans ephedrans A, B, C, D and E were isolated from *Ephedra distachya* herbs, which have been confirmed to have anti-hyperglycemic activity to alloxan-induced diabetic mice (Konno et al., 1985a,b,c,d,e). The alkaloid extract of *Ephedra distachya* herbs and L-ephedrine showed suppression on the hyperglycemia of diabetic mice induced by streptozotocin. The mechanism may be to regenerate atrophied pancreatic islets, restore the secretion of insulin, and thus correct hyperglycemia (Xiu et al., 2001).

4.4.5. *Agrimonia pilosa Ledeb. (Rosaceae)*

Used solely as a secret recipe to treat diabetes. The clinical reports showed that diabetes of some patients even disappeared (Wang and Guo, 1992; Dong, 1994). The extract of the herb was experimentally proved to be effective to lower blood glucose in normal and alloxan-induced diabetic mice (Li et al., 2002).

4.4.6. *Anisodus tanguticus (Maxim.) Pascher (Solanaceae)*

Used for the treatment of type 2 diabetes by Chinese doctors. Be effective to improve the complications while lowering blood glucose.

4.4.7. *Catharanthus roseus (L.) G. Don (Apocynaceae)*

The extract of *Catharanthus roseus* leaves has a remarkable effect to lower blood glucose (Chattopadhyay, 1999; Singh et al., 2001). The medicinal preparations of this plant have been developed to treat diabetes in clinic instead of the use of insulin in Eastern Asia and Southern Africa. The active constituents are alkaloids vindoline, vindolinine and vleurosine (De and Saha, 1975).

4.4.8. *Stevia rebaudina (Bert.) Hemsl. (Compositae)*

The natural sweetener stevioside, which is found in the plant *Stevia rebaudiana* Bertoni, has been used in the treatment of diabetes for many years in many parts of the world. Stevioside with the mechanism to stimulate insulin secretion via a direct action on β-cells of pancreatic islet is considered to have the potential of becoming a new antidiabetic drug for use in type 2 diabetes (White et al., 1994; Jeppesen et al., 2000, 2002).

4.4.9. *Psidium guajava L. (Myrtaceae)*

The aqueous extract of *Psidium guajava* leaves has a good effect to lower blood glucose (Cheng and Yang, 1983; Maruyama et al., 1985; Basnet et al., 1995; Deguchi et al., 1998). Flavonoid glycosides such as strictinin, isostrictinin and pedunculagin are the effective constituents, which have been used in clinical treatment of diabetes to improve the sensitivity of insulin (Maruyama et al., 1985). A glycoprotein with the molecular weight of 50,000–100,000 was also identified as active component for anti-diabetes (Basnet et al., 1995).

4.4.10. *Aralia elta (Miq.) Seem. and Aralia decaisneana Hance (Araliaceae)*

The bark of branches and roots of *Aralia elta* and *Aralia decaisneana* Hance was used to treat diabetes. Triterpenoids and their glycosides are the active components to lower the level of total serum cholesterol, glucose and triglyceride in normal and diabetic animals (Wang et al., 1995; Kim and Im, 1999). Some triterpenoids and their glycosides with anti-hyperglycemic activity have been isolated. It concerns oleanolic acid, 16-β-hydroxy-18-β-D-oleanolic acid, oleanolic acid-28-*O*-β-D-glucopyranoside, 16-β-hydroxy-18-β-D-oleanolic acid-28-*O*-β-D-glucopyranoside and ursolic acid (Kim et al., 1993; Yi et al., 1997; Lin et al., 2000). Some aliphatic compounds, including pentadecanoic acid, hexadecanoic acid, octadecanoic acid, eicosanoic acid, docosanoic acid, tetracosanoic acid, hexacosanoic acid, 1-hexacosene and hexacosanol were also isolated and identified as active components for anti-diabetes mellitus (Watanabe et al., 1977).

4.4.11. *Caesalpinia sappan L. (Leguminosae)*

Caesalpin P, sappanchalcone, 3-deoxysappanone, brazilin, and protosappanin A have been isolated and identified as aldose reductase inhibitors to be useful for the treatment of diabetic complications, of which, sappanchalcone at a dose of 10^5 mol/l can inhibit 84% of aldose reductas (Moon, 1986; Moon et al., 1988; Morota et al., 1990). Some preparations have been put into clinical use (Moon, 1986; Morota et al., 1990).

4.4.12. *Rhodiola sachalinensis A. (Crassulaceae)*

This plant is used in traditional Chinese medicine as tonic medicine, which is considered helpful for diabetes care. Some research results showed that polysaccharides are the active principles of anti-diabetic activity (Cheng et al., 1993).

4.4.13. *Eriobotrya japonica (Thunb.) Lindl. (Rosaceae)*

Eriobotrya japonica was found to possess a marked hyperglycemic action to normal and alloxan-diabetic rabbits and mice (Noreen et al., 1988; Roman-Ramos et al., 1991; El-Hossary et al., 2000). The further studies, carried out by De Tommasi et al. (1991) and Ivorra et al. (1988), showed that sesquiterpene glycosides and polyhydroxylated triterpenoids are the active constituents for controlling diabetes mellitus. The anti-diabetic mechanism may be to promote insulin secretion.

4.4.14. *Amorphophallus spp. (Araceae)*

Several species of the genus *Amorphophallus* Blume. ex Decne, *Amorphophallus rivieri* Durieu, *Amorphophallus konjack* K. Koch. and *Amorphophallus sinensis* Belval, are traditionally used as healthy diets for weight loss and diabetes care in many parts of China. There are many *Amorphophallus* products on the market in China, of which, *Amorphophallus konjack* fine powder was experimentally

proved to be effective to lower blood glucose of animals or humans (Mao et al., 1999). The active compounds are konjack oligosaccharides and galactomannan (Garcia et al., 1988; Yang et al., 2001).

4.4.15. Oenothera erythrosepala Borb. (Oangraceae)

The dose of 15 g/100 ml of evening primrose oil can lower the fasting blood glucose in experimental animals, with a effect rate of 78% (Xu et al., 1994).

4.4.16. Tribuluks terrestris L. (Zygophyllaceae)

The extract of *Tribuluks terrestris* significantly decreased blood glucose level in normal and alloxan-induced diabetic mice, increased serum insulin level in alloxan-induced diabetic mice, and improved glucose tolerance of normal and alloxan-induced diabetic mice (You and Wang, 2000).

4.4.17. Euonyrnus alatus (Thunb.) Sieb. (Celastraceae)

Some research results on the chemistry, pharmacology and clinical use indicated that this plant possesses an activity to lower blood glucose and lipid (Qi et al., 1998; Yao et al., 2000). It is a promising natural source to be developed for the treatment of diabetes mellitus.

4.4.18. Nelumbo nucifera Gaertn. (Nymphaeaceae)

The root nodes of lotus are used in China to treat diabetes by folk patients. Modern pharmacological and chemical research results supported the use. Oral administration of the ethanolic extract of *Nelumbo nucifera* rhizomes can markedly reduce the blood sugar level of normal, glucose-fed and streptozotocin-induced hyperglycemic rats (Mukherjee et al., 1997). The activity-guided isolation resulted in the isolation of tryptophan from the node of lotus rhizome. The pharmacological tests showed that tryptophan could lower the blood glucose level significantly in glucose-fed hyperglycemic mice and exhibited over 44% of activity compared with tolbutamide (Lee et al., 2001). The crude protein isolated from lotus seeds, a tonic nourishment and medicine, also caused a significant decrease in the blood glucose level of diabetic albino rats after 2 weeks of treatment (Ibrahim and El-Eraqy, 1996).

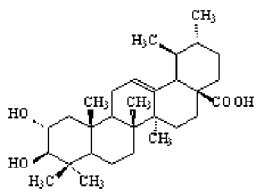
5. Chemical constituents with anti-diabetic activity isolated from traditional Chinese medicines

Based on a large number of chemical and pharmacological research work, numerous bioactive compounds have been found in Chinese medicinal plants for diabetes (Chen, 1987; Wu and Li, 1992; Gu and Jiang, 1997; Yin and Chen, 2000). These compounds include polysaccharides, terpenoids, flavonoids, sterols and alkaloids, and some others, some of which have been developed as new drugs and used in clinical treatment of diabetes in China.

5.1. Terpenoids

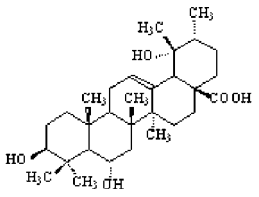
There are many compounds, isolated from medicinal plants with anti-diabetic activity, of which, triterpenoid saponins are the promising compounds with potential to be developed into new drugs for anti-diabetes.

(1) Triterpenoids: ginsenoside, senticoside A, boussingoside and momordin (from *Boussingaultia baselloides*), kikyosaponin, timosaponin, 3,6,9-trihydroxyurs-12-en-28-oic acid and 2,3-dihydroxyurs-12-en-28-oic acid (from *Eriobotrya japonica*), oleanolic acid (from *Ligustrum lucidum*), tormentic acid (from *Eriobotrya japonica*), ursolic acid (from *Punica granatum* and *Cornus officinalis*), gymnemagenin, gymnemasaponin, gymnemic acid, and gymnemosides.



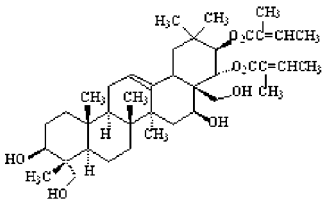
2,3-dihydroxy-urs-12-en-28-oic acid

(From *E. japonica;* De Tommasi et al., 1991)



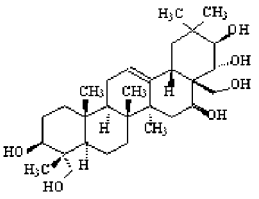
3,6,9-trihydroxy-urs-12-en-28-oic acid

(From *E. japonica;* De Tommasi et al., 1991)



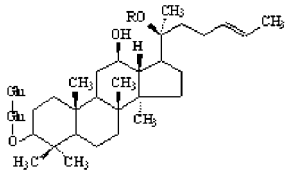
Gymnemic acid V

(From *G. sylvestre;* Yoshikawa et al., 1993)



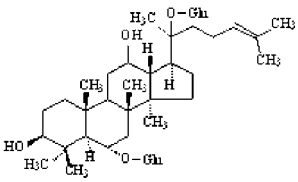
Gymnemagenin

(From *G. sylvestre;* Yoshikawa et al., 1993)



Ginsenoside

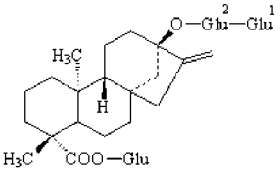
(From *P. ginseng* and *C. pentaphyllum;* Yamasaki, 1995; Lee et al., 1997,1998; Kitamura et al., 1997)



Senticoside A

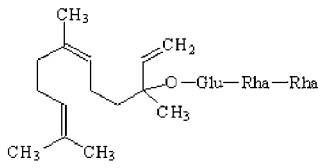
(From *A. senticosus;* Ni et al., 1987)

(2) Diterpenoids and sesquiterpenoids: stevioside, salvin, salvicin and salvifolin (from *Salvia japonica* Thunb.).



Stevioside

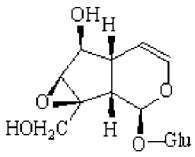
(From *S. rebaudiana;* White et al., 1994; Jeppesen et al., 2000,2002)



Proloquatifoligenin IV

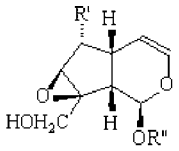
(From *E. japonica;* De Tommasi et al., 1991)

(3) Monoterpenoids: mainly iridoid glycosides, such as catalpol, rehmannioside A, B, C, and D.



Catalpol

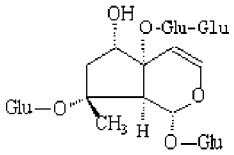
(From *R. glutinosa;* Nishimura et al., 1991)



Rehmannioside A, B

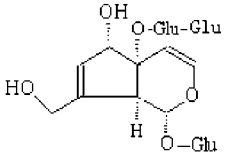
A: R' = OH R'' = Glu-Glu **B**: R' = O-Glu R'' = Glu

(From *R. glutinosa*; Coshio and Inouye, 1982)



Rehmannioside C

(From *R. glutinosa*; Coshio and Inouye, 1982)



Rehmannioside D

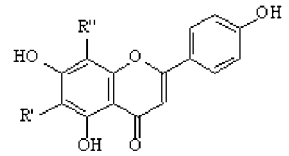
(From *R. glutinosa*; Coshio and Inouye, 1982)

5.2. Polysaccharides

Many kinds of polysaccharides have been isolated from traditional Chinese medicines for anti-diabetes, most of which performed a good effect. Examples are panaxan, laminaran, coixan, pachymaran, anemarn, moran, lithosperman, trichosan, saciharan, ephedran, abelmosan, atractan.

5.3. Flavonoids

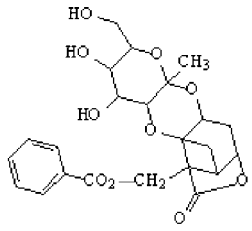
Some flavonoids have been isolated from traditional Chinese medicines for anti-diabetes. Most of them showed a mechanism to improve the function of β-cells of pancreatic islet. Examples include kakonein, 7-(6-*O*-malonyl-D-glucopyranosyloxy)-3-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one, flavone C-glycoside, icariin, neomyrtillin, sappanchalcone, caesalpin P, 3-deoxysappanone, protosappanin A, brazilin, swerchirin (from *Swertia chirayita* (Roxb ex Flem) Karst) and hyperin (from *Tilia cordata* Mill.).



Flavone C-glycosides

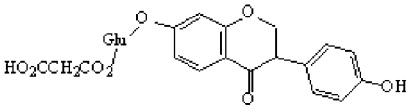
R' = C-β-D-xylopyranosyl,
R'' = C-β-D-galactopyranosyl

(From *P. ternata;* Nishimura, 1992)



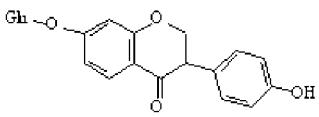
Lactiflorin

(From *P. veitchii;* Hsu et al., 1997)



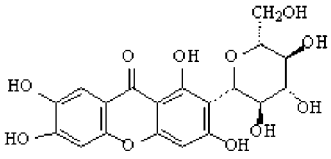
7-(6-O-malonyl-β-D-glucopyranosyloxy)-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one

(From *P. lobata;* Hirakura et al., 1989)



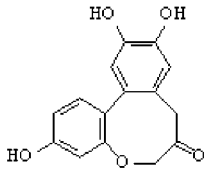
Kakonein

(From *P. lobata;* Hirakura et al., 1989)



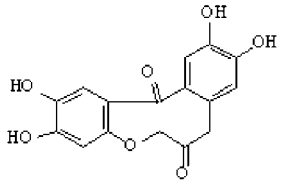
Magniferin

(From *A. asphodeloides*; Miura et al., 2001)



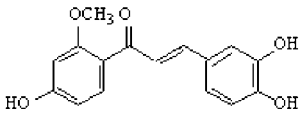
Protosappanin A

(From *C. sappan;* Moon et al., 1986; Morota et al., 1990)



Caesalpin P

(From *C. sappan;* Moon et al., 1986; Morota et al., 1990)



Sappanchalcone

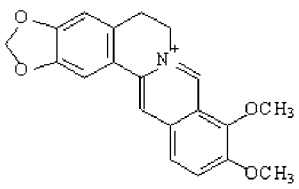
(From *C. sappan;* Moon et al., 1986; Morota et al., 1990)

5.4. Insulin-like compounds, polypeptides and amino acids

These substances performed excellent an effect for the treatment of diabetes. Examples include p-insulin (bitter gourd polypeptide, from *Momordica charantia*), ginseng glycopeptides, α-methylenecyclopropylglycin (from *Litchi chinensis* Sonn.), *S*-allyl cysteine sulfoxide (from *Allium sativum*).

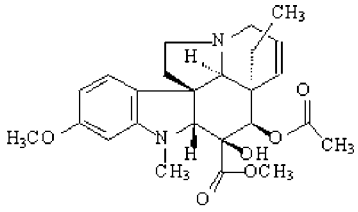
5.5. Alkaloids

A few compounds were isolated toward diabetes, which performed excellent effect. Such as berberin, anisodamine, vindoline, vindolinine, leurosine, aconitine, hanfangchin A (from *Stephania tetradra* S. Moore) and multiflorine (from *L. hirsutus*).



Berberine

(From *C. chinensis;* Chen et al., 1986)



Vindoline

(From *C. roseus;* De and Saha, 1975)

5.6. Sterols

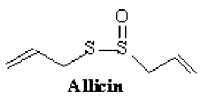
The hypoglycemic effect is similar to sulfonylurea-like medicines. An example is charantin (from *Momordica charantia*).

5.7. Unsaturated fatty acids

The efficacy of anti-hyperglycemia is strong but the effectiveness is shown slow. Examples are linoleic acid (from *Bombyx mori*) and trihydroxyljecoric acid (from *Bombyx alba* L.).

5.8. Miscellaneous

Compounds with a sulfur bond, such as allicin and allyl propyl disulfide, and 3-hydroxy-3-methylglutaric acid (from *Tillandsia usneoides*), sodium oxaloacetate (from *Euonyrnus alatus* (Thunb.) Sieb.), edyson (from the leaf of *Morus alba* L.) are examples of active compounds with a varied structure.



Allicin

(From *A. sativum;* Augusti et al., 1996)

6. Prospect of traditional Chinese medicines for diabetes mellitus

6.1. Paying much attention to discover natural drugs from traditional Chinese medicines

Natural drugs from traditional Chinese medicine are gaining popularity because of several advantages such as often fewer side-effects, better patient tolerance, relatively less expensive and acceptance due to a long history of use. The more important cause is that natural products, especially herbal medicines provide rational means for the treatment of many diseases that are obstinate and incurable in other systems of medicine. Therefore, a revival of interest in the use of plants in pharmacy world-widely emerges from both the pharmaceutical industry as a source of new lead molecules and the general public who are using plant extracts in many ways in conventional and complementary therapies.

In the use of several thousand years in China, the traditional Chinese medicine has built up a characteristic medical system. From aristocrats to common people, it was well known that natural medicines with different functions could be used to protect their health. The rich plant resources are the strong backing of traditional Chinese medicines. The data collected through a national scale investigation showed that there are more than 11,000 plant species indigenously used as Chinese medicines for various diseases in different parts of China, of which, only 10–15% are recorded in medical literature and appear in market as commodities. A large number of plants were always used as folk herbs and secret recipe for different illnesses. Some recipes were only locally known, even some of which were only inherited from generation to generation in certain Chinese doctor's family. These plants often have a distinctive effect for some diseases including diabetes mellitus. In addition, about 1580 species of animals and insects are also used in traditional Chinese medicine. The ethnic medicines and ethnotherapies also are an important part of the treasures in Chinese traditional medicine, which are always used for their characterized therapies by minorities in ethnic regions, such as Zang, Mongolia, Uygur, Dai and Zhuang.

So, it must have an interest to discover new lead compounds for future drug development from the traditional Chinese medicines with definite functions which have not been developed. A special focus should be put on the folk herbs

and folk therapies for the treatment of diabetes and other diseases.

6.2. Screening and developing natural anti-diabetic agents from Chinese traditional medicinal plants

Although chemical and biochemical hypoglycemic agents, e.g., insulin, tolbutamide, phenformin, troglitazone, rosigitazone and repaglinide, are the mainstay of treatment of diabetes and are effective in controlling hyperglycemia, they have prominent side-effects and fail to significantly alter the course of diabetic complications. Some traditional Chinese medicines appear to be effective for both the control of blood glucose and the modification of the course of diabetic complications without side-effects.

Plants have always been an exemplary source of drugs. Plants have yielded directly or indirectly many important medicines in the past. For diabetes, for example, the discovery of the widely used hypoglycemic drug, metformin, came from the traditional approach of using *Galega officinalis*. The traditional Chinese medicines, all of which come from nature products, are thought to treat diabetes through improving the immunity of the body. This is a good therapeutic procedure, which is different from western medical science. In the Chinese traditional medicine, many of traditional Chinese medicines are found to be very effective for diabetes treatment when they are single used. In this case, the effect often means reducing blood sugar, which is same as western medicines. These traditional Chinese medicines have great potential for scientists to find active compounds and develop new drugs for anti-diabetes. Many Simple Recipes and Compound Recipes have been shown to possess several hypoglycemic mechanisms to treat complication while lowering blood glucose, some ones even possess activity to regulate blood glucose two-dimensionally. These Chinese medicines are a potential source of anti-diabetic drugs because of their remarkable efficacy, rich resources and the characteristic anti-diabetic mechanisms. The clinical practice from hospital and folk experience has shown the possibility to obtain natural products to recover diabetes and its complications from traditional Chinese medicinal plants.

Thus, there is an increasing requirement and the feasibility to screen and obtain active compounds including plant extracts from Chinese traditional medicinal plants for the treatment of diabetes and its complications.

6.3. Carrying out further phytochemical and pharmacological research to normalize the traditional Chinese medicines with definite anti-diabetic activity

Compound Recipes are often used by Chinese doctors. Almost all of the Chinese medicinal preparations were made according to the Compound Recipes only with clinical experience for miscellaneous diseases. Chinese medicinal preparations from Compound Recipe are acceptable for eastern people, but not acceptable for western people. What should be done to make western people to accept Chinese medicinal preparations? One way is to introduce traditional Chinese medical knowledge to western people, make them understand more traditional Chinese medical theory. Another way is to standardize Chinese medicinal preparations, find more scientific and experimental evidences through research work on effective constituents, toxicity, pharmacokinetics, effectiveness and efficacy, etc., so that western people improve belief in Chinese medicinal preparations.

The lack of scientific and experimental evidence about effective constituents, toxicity, pharmacokinetics, effectiveness and efficacy resulted in deficiency of belief in effectiveness, quality and safety of Chinese medicines. The need for adequate standards of herbal preparations to ensure quality, safety and efficacy has been highlighted since the use of herbal medicines and phytotherapies.

This requires biological testing of plant extracts, isolation of bioactive components, as well as toxicological, pharmacodynamical and, ultimately, clinical studies. For Chinese medicinal preparations, which are made from plant extracts, and often considered to be effective due to a mixture of active ingredients rather than a single constituent, standardization is difficult, furthermore, possible to lose active principles. However, the standardization is an absolute requirement.

It is a significant work to isolate active components of Chinese medicinal plants with confirmed hypoglycemic activity, to explain their pharmacological mechanism, and lastly, develop normalized Chinese medicinal preparations for anti-diabetes and it complications.

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