Pharmacology and Phytochemistry of Pakistani Herbs and Herbal Drugs Used for Treatment of Diabetes

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Abstract: After twenty years Pakistan will be the fourth largest country with respect to the diabetic individuals. For a developing country like Pakistan availability of modern medical facilities to every person is not possible. In addition to economic constrains, reported side effects of these modern drugs encourage us to search for an economical and safe alternative that can cure this disease. Herbal plants (cheaper availability and with less or no side effects) have emerged as a potential candidate. This review focuses the effectiveness of herbs and herbal drugs which are commonly used in Pakistan against diabetes. Different search engines were explored including Pubmed, Google and Asci database (up to 2nd June 2011) by using different keywords. Priority was given to research article and information given by authentic organizations and federations. Nineteen plants, which were used by local people as vegetable or herbal remedy, were analyzed for their antidiabetic potentials on the basis of previously published literature. Varying levels of antioxidant, antihyperlipidemic, Insulin stimulating, nephroprotective and hepatoprotective activities of these plants have been reported in various studies. O. sanctum, Z. officinalis, T. foenum-graecum and P. amarus were found to be most effective against diabetes. In future adaptive use of these herbs in daily life as food may help to slow down the pace of disease development in Pakistan. There are plenty of herbs for which the medicinal value is still to be inquired so that they can replace and used as an alternate of synthetic drugs.

Key words: Herbal remedies, diabetic complications, antioxidant mechanism, oxidative stree, toxicity

INTRODUCTION

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin (a drug used for the treatment of diabetes) or when the body cannot effectively use the insulin it produces (http://www.who.int/diabetes/en/) (last time accessed on 27 April 2011). If untreated, it could result in kidney and heart disease, stroke, blindness, loss of limbs and reduced life expectancy (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). There are mainly three types of diabetes type 1, type 2 and gestational diabetes mellitus (Alberti and Zimet, 1998). Genetics plays an important role in the development of both type 1 and type 2 diabetes (Cooke and Plotnick, 2008). Destruction of insulin producing beta cells of pancreas either by patient’s own immune system or due to other factors ultimately results in the occurrence of type 1 diabetes (Cooke and Plotnick, 2008; Ylipaasto et al., 2004). Destruction of beta cells is thought to be triggered by a combination of different environmental factors in genetically susceptible organisms. Type 2 diabetes is most prevalent among diabetic patents and is directly linked with individuals suffering with a physiological disorder of insulin resistance (Kahn et al., 2006). Factors like genetic susceptibility of patient, diet and other environmental condition eventually leads towards the development of type 2 diabetes (Riserus et al., 2009; Ripsin et al., 2009). Another form of diabetes, which only linked to females, is Gestational Diabetes Mellitus (GDM). This form of diabetes is characterized as detection of increased blood glucose levels during pregnancy (American Diabetes Association, 2010). In a study of Australian population it was found that age of women positively correlates with the occurrence of this disease (Templeton and Piers-Caldwell, 2008). Individuals suffering with this form of diabetes are more prone to type 2 diabetes (Hoffman et al., 1998).

STATUS OF DIABETES IN PAKISTAN

Around 180 million people worldwide suffer from diabetes, and the number is predicted to reach 325 million by the year 2025 (Leibelvyr, 2005). In 2007, 246 million people world-wide suffered from diabetes and this number
makes the disease as one of the most widespread global
disease and 4th leading cause of death in the world.
Report of IDF published in The Nation, November 15,
2008. Almost 438 million people will suffer from diabetes
in 2030 compare to 177 million in 2010 (Report by WHO
com/people_worldwide_suffer_from_diabetes_future_health.html). Among the 246 million diabetic
people worldwide approximately half are from Asian
countries (http://www.asiandiabetes.org/). In the list of
ten most vulnerable countries (in term of number of
people with diabetes) of 2030 seven are from Asia
(Wild et al., 2004). It is also very alarming that diabetics
develop in younger age in Asian population than the
white peoples (Ramachandran et al., 2010).

Pakistan is the 7th leading diabetic nation in the
world and if this trend keeps on increasing at same pace
then after 20 years it will be ranked as 4th largest country
with respect to diabetes (http://ndpppk.com/dip.html). In
Pakistan 6.9 million people are affected by diabetes and
this number will rise up to 11.5 million by 2025 (Hayat and
Shaikh, 2010). According to International Diabetic
Federation, prevalence of diabetes is more in urban areas
than rural, males are more prone to this disease than
females, and among the age groups “40-59” was having
maximum percentage of diabetic individual in Pakistan.
Among four provinces of Pakistan, perverseness of
diabetes in adults was found to be highest in Sindh
followed by Punjab, Balochistan and Khyber Pakhton
Khwa (http://ndpppk.com/dip.html)
(last accessed on 28-4-2011). Coordinated efforts from
public and private sectors are required to fight against
this chronic disease.

HERBAL REMEDIES

Every plant could be a medicinal plant? No, according to WHO (1977) a medicinal plant is any plant
that can be used to synthesize valuable drugs as one or
more of its organs contain substances that can be useful
for medicinal purpose. According to World Health
Organization more than 21,000 plants are being in use as
medicinal purpose around the world. A huge part of
world’s population (80%) employs herbal medicines to
deals with their daily medical issues (DaSilva et al., 2002).
Twenty five percent of drugs prescribed by Western
pharmacists comprise of elements that are of plant origin.
Studies aiming at the development of rapidly propagating
methods for medicinal plants is an indication that demand
for these plant is increasing (Nalawade and Tsay, 2004;
Huang et al., 2000; Khan et al., 2004; Malik et al., 2007;
Banu and Bari, 2007; Jamil et al., 2007; Ganta et al., 2010;
Satyavani et al., 2011a). Use of herbal medicines is also
very common among population of Pakistan (Hoareau and
DaSilva, 1999). Medicines based on herbal formulations
usually have lesser side effects and better compatibility
with human body than modern medicines (Kamboj, 2000).
All those diseases like memory loss, osteoporosis,
diabetic wounds, alzheimer, immune and liver disorders
etc. which are not completely or partially curable with
modern medicines are being treated with herbal medicines
(Gessner et al., 1985; Watanabe et al., 2001; Kamboj,
2000). Less side effects, better compatibility and only
available treatment for some diseases makes the herbal
medicines an ideal remedy for treatment of the diseases.

NEED AND SCOPE OF HERBAL REMEDIES
FOR DIABETES TREATMENT

There are different methods to treat diabetes with
varying degree of success like use of different drugs
(intensive insulin therapy (IIT) (Qaseem et al., 2011;
Clement et al., 2004), antibodies (monoclonal antibody
(Herold et al., 2002)) and organ transplantation
(Ryan et al., 2001). Islet transplantation is one of the
surgical methods used to treat type 1 diabetes. In a study
by Guignard et al. (2007) a total of 87, 620 were calculated
for one islet transplantation. Type 2 diabetes is not insulin
dependent and many different drugs have been employed
to treat this disease. Metformin is a drug used to treat
type 2 diabetes. Long term use and high doses of this
drug are associated with malabsorption of vitamin B12 and
lactic acidosis development, respectively (Bailey and
Turner, 1996; Salpeter et al., 2006). Some drugs like
sulfonylureas and thiazolidinediones were used to treat
type 2 diabetes and found to be linked with hypoglycemia
and increase in both body weight along with increased
risk to develop cardiovascular disease (Groop, 1992;
Meinert et al., 1970; Kuhn et al., 2006; Singh et al., 2007).
Glimides and α-Glucosidase inhibitors are also used to
treat non-insulin dependent diabetes; frequent
administration of these drugs is required to reduce the
glucose levels in blood (Malaisse, 2003; Van de Laar et al., 2005). Each drug have some
disadvantages like chances of developing other diseases,
so frequent and careful administration of these drugs
should be considered as all of above drugs are very
expensive (Nathan et al., 2009). In a country like Pakistan
where low value healthcare practices has been performed
and 24% of its population lives below the line of poverty,
treatment of diabetes with expensive drugs and surgical
methods is not feasible (https://www.cia.gov last time
access on 20-03-2011). So in Pakistan being a developing
country use of herbs is inevitable as a cheaper source of
medication to treat highly prevalent disease such as
diabetes.
Pharmacological characteristics and phytochemistry of Herbs and Herbal Drugs used for the treatment of Diabetes is given below:

**Allium cepa:** *Allium cepa* L. is the common onion that belongs to family Alliaceae (Rose et al., 2005; Nithya and Ramachandramurty, 2007). Mainly onion bulbs are white, yellow or red, stems are green and leaves are hollow (Farooqi and Kumar, 2003). It is a cultivated crop in various areas of Pakistan (Malik et al., 2003) and its juice is used as a remedy to treat diabetes and high blood pressure (Ahmad et al., 2009). Antifungal and antioxidant properties of its extract are also well proven (Tagoe et al., 2011; Ige et al., 2011). Onion is a rich source of dietary flavonoids (Slimestad et al., 2007; Sharif et al., 2010). Some flavonol glycosides of onion were found to be very stable under commercial storage conditions (Price et al., 1997). Flavonol glycosides are thought to have antidiabetic activity due to their inhibitory effect on glycation (Kim et al., 2004). Maillard reaction is a part of human glycation process (Horiuchi et al., 1991). Kousar et al. (2008) found negative effect of onion extract on maillard reaction. So this inhibitory effect on maillard reaction could be one of the factors contributing for its antidiabetic effect. Different sulfur containing compounds also contribute for antidiabetic activity of onion. This was confirmed by Kumari et al. (1995) who studied the antidiabetic effect of an amino acid (S-methyl cysteine sulfoxide) isolated from onion. They found that the results were significant in lowering the blood glucose levels of rats. This compound was also found to have anti-hyperlipidemic activity (Kumari and Augusti, 2007). Consumption of onion in large quantity could have serious health hazards as some compounds possess inhibiting effects on thiol group enzymes (Augusti, 1996). Diet consisting of 6% *Allium cepa* resulted in impaired growth of male Wistar rats (Abdel Gadir et al., 2006), no harmful effect was observed on 2% diet (Abdel-Gadir et al., 2007).

**Allium sativum:** *Allium sativum* (garlic) is a herb bearing an underground bulb made up of glossy cloves that are used all over the world to reduce the vulnerable effects of most of the diseases. Garlic is also used in food as flavoring agent and spice, its strong order and flavor is due to the presence of sulphur compounds (Thomson et al., 2007). Antioxidant, antifungal, antimicrobial and antidiabetic properties of its extract has been reported in many studies (Avci et al., 2005; Ogungbe and Lawai, 2008; Abera et al., 2011; Butkup and Samapito, 2011; Masaadeh et al., 2006; Philip et al., 2009; Shokrzadeh and Ebadi, 2006; Hasan et al., 2005; Sukandar et al., 2010). It is locally known as “Thoom” and its underground part is used for diabetes and hypertension (Ahmad et al., 2009; Ishtiaq et al., 2007). A range of compounds (alkaloids, amino acids, carbohydrates, cardiac glycoside, flavonoids, ketones, lipids, phenol, reducing sugars, saponins, steroids, terpene) are present in it (Otusami and Amadi, 2009; Pathmanathan et al., 2010; Mikail, 2010). Kumar and Reddy (1999) studied the effect of ethanol extract of garlic on alloxan induced diabetic mice. They found significant decrease in blood glucose levels. Garlic contains a variety of sulfur based compounds, which are mainly in the form of cysteine derivatives (Augusti, 1996). A sulfur containing amino acid (S-allyl cysteine sulfoxide) isolated form *Allium sativum* showed significant antidiabetic activity in alloxan diabetic rats (Sheela and Augusti, 1992; Augusti and Sheela, 1996). Its antidiabetic activity was almost same as those of glibenclamide and insulin. In addition better performance of this compound as hypolipidemic agent makes it more appropriate to deal with both diabetes and hyperlipidemia. Diet consisting of 6% *Allium sativum* produced impaired growth in male Wistar rats (Abdel Gadir et al., 2006).

**Aloe vera:** *Aloe vera* is being used as medicinal plant since many years (Subramanian et al., 2006a,b, 2007). Leaves of this plant are green resembles with cactus leaves and filled with a clear gel like fluid, which is viscous in nature (Singh et al., 2010). In addition to its medicinal values it is also employed in poultry, dairy and as insecticide (Moorthy et al., 2009; Memerele, 2011; Odo et al., 2010; Oparaeke and Kuhlep, 2006; Panesar and Shinde, 2011). Different type of anthraquinones, sacarides, vitamins, essential and nonessential amino acids, enzymes and inorganic compounds are present in *Aloe vera* (Vogler and Enst, 1999). Leaves are the main part, which contains most of these compounds (Okamura et al., 1997; Okamura et al., 1998; Vogler and Enst, 1999; Ni et al., 2004). Locally *Aloe vera* is known as “Kunwarghandel” and is used as an ingredient of herbal formulation used to treat the diabetes (Ahmad et al., 2009). Rajasekaran and Sathishsekar (2007) reported that *Aloe vera* gel extract is potential agent in preventing the glycoprotein’s mediated secondary diabetic complications in experimentally induced diabetic rats. Choi et al. (1996) isolated aloe-emodin and different form of aloins (aloin A and B) from freeze dried *Aloe vera* leaves. Nidiry et al. (2011) also reported that aloin and aloe-emodin are main constituents of *Aloe vera* extract. Perez et al. (2007) studied the effect of aloe extract containing high concentrations of aloin and aloe-emodin on experimentally induced insulin resistant mice. They found significant
decrease in blood glucose levels along with protective effect on insulin producing β cells. It can be concluded that these compounds are major contributors for antidiabetic activity of Aloe vera. Due to the presence of gibberellic-like active substances it showed anti-inflammatory activity in diabetic animals (Davis and Maro, 1989). Protective effects of its extract on β cells make it more suitable for the treatment of type I diabetes. Pritham and Kale (2007) stated that a significant decrease in antioxidant activity of Aloe vera was observed when it was infected with Alternaria alternata. So before any medicinal use of plant it should be checked for any kind of phyllosphere toxicity.

Artemisia herba-alba: Artemisia herba-alba commonly known as white wormwood is a dwarf shrub that usually grows in arid areas. Leaves of this plant have pungent smell and are covered by woolly hairs (Salido et al., 2004). Antioxidant properties of this plant are well reported (Al-Mustafa and Al-Thunibat, 2008). Sterol, terpene and alcohols have been reported from aerial parts and essential oil of this plant (Laid et al., 2008; Kalemba et al., 2002). Aqueous extract of aerial parts administrated at the rate of 0.39 g kg⁻¹ body weight results in significant reduction of blood glucose levels in both diabetic rats and rabbits (Al-Shamaony et al., 1994). Khafagy et al. (1971) isolated the santonic and stigmasterol from flowering branches of Artemisia herba alba. Santonic has been banned in USA due to its potential toxicity (Fadhil, 2008). On administration of stigmasterol in mice a reduction in blood glucose and an increase in insulin concentration was observed (Panda et al., 2009). Artemisia herba-alba is an ingredient of hyponidd (herbomineral formulation) and this formulation is reported for both antidiabetic and antioxidant activity (Subash-Babu and Ignacimuthu, 2007). Presence of stigmasterol as an active compound of this formulation further supports its application as antidiabetic agent. Almasad et al. (2007) reported the adverse effect of Artemisia herba alba on reproductive system of female Sprague-Dawley rats.

Catharanthus roseus: Catharanthus roseus L. (G. Don) is an important medicinal plant of family Apocynaceae (Jalecl et al., 2009). Its extract showed a considerable wound healing, anti-tumor, hypotensive and antifungal activity (Nagori and Solanki, 2011; Rama et al., 2004; Ara et al., 2008; Saravanan and Valluvaparidasan, 2001). It is locally known as “Sada bahar” and used to deal with diabetes (Ahmad et al., 2009). Jarald et al. (2008) proved that leaf extract have more strong antihyperglycaemic activity as compared to extracts of other plant parts (stem, flower and root). Habib et al. (2005) also reported hypoglycemic effect of its leaf extract on normal rats. The aqueous extract of its leaves at the dose of 5000 mg kg⁻¹ showed significant improvement in different physiological/histological parameters, which were altered after the onset of diabetes in streptozotocin induced diabetic rats (Prasad et al., 2009). Nammi et al. (2003) studied the effect of leaf juice extract of Catharanthus roseus on blood glucose levels of alloxan-induced diabetic rabbits. They found strong and long lasting antidiabetic effect of its extract in comparison with glibenclamide. They further concluded that its active ingredient might have enhanced the insulin secretion from β-cells due to which reduction in blood glucose levels was observed in both diabetic and normal animals. Same hypoglycemic effect was also observed in streptozotocin induced rats (Ahmed et al., 2007). Leaves of this plant contain many compounds like chlorogenic acid, kaemferol trisaccharides, quercetin trisaccharides (Mustafa and Verpoorte, 2007). Chlorogenic acid was found to have hypoglycemic activity in mice (Nicasio et al., 2005). Flowers of this plant are also used for treatment of diabetes (Rahmatullah et al., 2009). Many types of flavonoid (Quercetin, Malvidin, Petunidin, Hirsutidin) have been reported to be present in its flower (Mustafa and Verpoorte, 2007). Quercetin (active component of flower) significantly reduced the plasma glucose levels in streptozotocin induced diabetic rats but showed no effect on normal individuals (Vessal et al., 2003). This antihyperglycemic effect is attributed to the increased insulin release as a result of quercetin regenerative effect on pancreatic islets. Siddiqui et al. (2010) studied the cytotoxicity of Catharanthus roseus fractions on Human Colon Colon Carcinoma Cell Line (HCT 116) and observed a dose dependent cytotoxic effect.

Cichorium intybus: Cichorium intybus have stalked leaves with more or less hairy stem and toothed scales (Rose, 1981). Its extract have shown antihypotensive, antiulcerogenic and antimicrobial properties (Hasan et al., 2007; Madani et al., 2008; Dugger and Gonuz, 2004; Rifat-uz-Zaman et al., 2006a; Rifat-uz-Zaman et al., 2006b). Powder obtained from the dried roots of Cichorium intybus (locally known as “Kashi”) is used to treat diabetes (Ahmad et al., 2009). Twenty percent decrease in blood glucose of streptozotocin induced rats was observed when administrated with ethanolic extract of Cichorium intybus, but there was no increase in blood insulin concentrations (Pushparaj et al., 2007). Presence of caffeoylquinic acids and chlorogenic acid in various part of Cichorium intybus have been reported (Milaia et al., 2009; Mulinacci et al., 2001). Mulinacci et al. (2001) characterized the chicoric acid and chlorogenic acid
from its leaves. This choric acid is reported as a potential antidiabetic agent with both insulin sensitizing and secretory property (Toussch et al., 2008; Andrade-Cetto and Wiedenfeld, 2001). Chlorogenic acid as an antidiabetic agent is useful for non-insulin-dependent diabetes (Hemmerle et al., 1997). Insulin (carbohydrate) present in almost all parts of plant (Milala et al., 2009) is reported to have potential beneficial effects as an antidiabetic agent against non-insulin-dependent diabetes (Yun et al., 2009). Quercetin is reported to have significant antidiabetic activity (Vessal et al., 2003). A variety of quercetins (quercetin-3-O-glucoside, quercetin-3-O-glucone, quercetin-3-O-β-D-glucuronide) has been reported as phytochemicals of this plant (Murica et al., 2001; Yang et al., 2009). Some of these have been analyzed for their antidiabetic activity as quercetin-3-O-glucoside was reported to have hypoglycemic effect in alloxan induced diabetic rats (Panda and Kar, 2007).

**Citrusus colocynthis**: Almost all parts of *Citrusus colocynthis* are used for various purposes in Pakistan (Mosam et al., 2008). Antidiabetic, antifungal, antibacterial, hypolipidaemic and local anesthetic activity of different plant parts extracts have been reported in various studies (Gurudeeban et al., 2010; Boulenou et al., 2009; Hadizadeh et al., 2009; Thrinaravukkarasu et al., 2010; Daradka et al., 2007; Ramanathan et al., 2011). Its extract is also used for the synthesis of nanoparticles (Satyavani et al., 2011). Extracts of different fruit parts were analyzed for their insulinotropic effects (Nnila et al., 2000). All of the tested extracts showed potential insulin secretory activity and authors concluded that the antidiabetic activity of fruit is due to the presence of different phytochemicals (β-pyrazol-1-ylalanine) in its seeds. To some extent aqueous seed extract was found to have positive effect on streptozotocin induced diabetic rats (Al-Ghafith et al., 2004). Isolation of various phytochemicals (alkaloids, flavonoids, glycosides, phenols, proteins, saponins) have been reported from its fruit (Najafi et al., 2010; Delazar et al., 2006). Antihyperglycemic activity of alkaloidal extract was non-significant in normal rabbits but glycosicid extract showed significant reduction in serum glucose levels (Abdel-Hassan et al., 2000). Saponin (plant phytochemical) also showed significant reduction in blood glucose levels in alloxan induced diabetic rabbits. Although this plant is been used as antidiabetic remedy but in a study conducted by Wafsi (1994) no effect of leaves and pulp was observed on glucose levels in diabetic and non-diabetic rats. High dose of *Citrusus colocynthis* could induce liver fibrosis and hepatocyte necrosis when administered in rats and this toxic effect is dose dependent (Dehghani and Panjehshahin, 2006).

**Coriandrum sativum**: *Coriandrum sativum* is locally used for various purposes in Pakistan (Hamayun et al., 2005; Hussain et al., 2009). Various reports have reported its antioxidant and antihyperglycemic activity is well reported (Sultana et al., 2010; Wagensteet al., 2004; Kansal et al., 2011; Gallagher et al., 2003; Srinivasan, 2005). Its extract has shown insulin-stimulating activity and there are chances that this activity is controlled by more than one phyto-constituents of its extract (Gray and Flatt, 1999). β-carotene is reported as one of the five fractions of its plant extract (Guerra et al., 2005) and it was found to be effective in reducing the diabetic complications in alloxan induced diabetic rats (Arora et al., 1999).

**Cucurbita maxima**: *Cucurbita maxima* are annual herbaceous vines with yellow flowers having a climbing stem up to 12 m long (Winkler et al., 2005). It is locally known as “Wun” and its fruits are consumed as vegetables in NWFP, Pakistan (Jan et al., 2009). Saha et al. (2011) reported that methanol extract of aerial parts successfully reduced the fasting blood glucose levels in streptozotocin induced Wistar albino rats (Saha et al., 2011). Its fruit contain beta-carotene (Muntean and Rotar, 2010), which is a known antidiabetic compound (Arora et al., 1999). A range of sterols (25(27)-dehydroprotostersterol, clerosterol, isofluosterol, stigmasterol, sitosterol, campesterol and codisterol) and fatty acids are present in its seeds (Garg and Nes, 1984; Fokou et al., 2009). Stigmasterol, which is also present in its seeds, is known hypoglycemic agent (Panda et al., 2009). But Jamalan et al. (1994) observed no hypoglycemic activity of stigmasterol when tested without β-sitosterol. So presence of β-sitosterol in its seeds (Basaran et al., 1998) further affirms the claim that both compounds stigmasterol and β-sitosterol contribute towards the hypoglycemic activity of its seed. Compounds like beta-carotene, stigmasterol and β-sitosterol could be the major contributing factors for its antidiabetic activity.

**Elephantopus scaber**: *Elephantopus scaber* is a stiff, inflexible and wild perennial herb, 10-50 cm long and usually grows under shady places. From the ancient times it has been known as a medicinal herb used for the treatment of several diseases (Wang et al., 2004). It is reported in many Asian countries including Pakistan (Ho et al., 2009). Its leaf and root extracts showed significant reduction in glucose levels of alloxan induce diabetic rats along with a regenerative effect on islet β-cells (Daisy et al., 2007). Same effect of its crude extract on serum glucose was observed in addition to increased insulin concentration in streptozotocin induced
hyperglycemic rats (Jasmine and Daisy, 2007). Mohan et al. (2010) reported the presence of different steroids in its leaf and rhizomes extracts. A steroid, 28N°-or-22(R)Witha 6,23-trienolide isolated from its acetone extract showed significant antidiabetic activity in streptozotocin induced diabetic rats (Daisy et al., 2009). Its regenerative effect on islet β-cells could be the most probable mode of action for its antidiabetic activity.

_Equisetum arvense_: _Equisetum arvense_ is locally known as “Chihly” and used as herbal remedy to treat different diseases (Khan and Khatoon, 2008). Saffeyeh et al. (2007a) observed significant decrease in serum glucose levels of experimentally induced diabetic rats on administration of its extracts. Histological studies showed that this extract have regenerative effect on pancreas (Soleimani et al., 2007). Along with its antidiabetic activity its extract also showed renoprotective activity (Saffeyeh et al., 2007b). Phytochemicals of this herb are mainly categorized as flavonoids, alkaloids, minerals, phenolic pterocarins, triterpenoids, saponins and phytosterols (Santhi et al., 2010). Glycation inhibitors are useful in diabetes treatment as advanced glycation end products (AGEs) are abundantly present in diabetic people and increase in AGEs are thought to be linked with complication in diabetes (Nakamura et al., 1997). Quercetin 3-O-β-d-glucopyranoside is a known glycation inhibitor (Jung et al., 2006) and it is reported as one of its active phytochemicals (Veit et al., 1993). Its regenerative effect on pancreas and glycination inhibition action could be the most probable mode of action for its hypoglycemic activity.

_Momordica charantia_: The immunostimulant, antidiabetic and anticancer properties of its extract are well reported (Prasad et al., 2006; Rahman et al., 2005; Tanaka et al., 2009; Asiamah et al., 2011). For successful treatment of diabetes people use fresh juice or powder of _Momordica charantia_ (Ahmad et al., 2009; Fatima et al., 2004). Leaf methanolic extract of _Momordica charantia_ has shown mild hypoglycemic effect on alloxan induced diabetic rats (Ataman et al., 2006). In another study its fruit methanolic extract has shown dose dependent hypoglycemic and anhtyglycemic effect in normal and diabetic rats, respectively (Kolawole et al., 2011). Seed aqueous extract significantly restored the altered enzymatic activities in streptozotocin induced diabetic rats (Sathishsekar and Rajasekaran, 2007). Srivastava et al. (1993) tested the hypoglycemic activity of both aqueous extract and dried powder of fruit on alloxan induced diabetic rats. They found significant decrease in blood glucose levels after three weeks on administration of aqueous extract but hypoglycemic effect of dried fruit powder was not significant. Fruit extract also showed enhanced insulin secretion from islets of langerhans and restored its histological architecture in alloxan induced diabetic rats (Fernandez et al., 2007). Ullah et al. (2011) reported that bitter gourd contain phytochemicals like tannin, flavonoids, terpenoids, cardiac glycosides, triterpin and sterol, resin, amino acid and phenolic compounds. Harinantena et al. (2006) identified two triterpene (5β,19-epoxy-3β,25-dihydroxycurcubita-6,23(E)-dien-9-ene and 3β,7β,25-trihydroxycurcubita-5,23(E)-dien-19-ol) as major compounds of dried fruit methanolic extract. Both of these compounds showed hypoglycemic effects in experimentally induced diabetic mice. A polypeptide (p-insulin) isolated from _Momordica charantia_ fruit effectively lowered the serum glucose levels in gerbils, langurs and humans (Khanna et al., 1981; Raman and Lau, 1996). Caffeic acid was identified as one of the phenolic compounds isolated from _Momordica charantia_ extract (Kubola and Srimanotrup, 2008). It is reported that under diabetic conditions the Glucose-6-phosphatase expression increases significantly (Liu et al., 2008). This catechin compound has down-regulatory effect on glucose-6-phosphatase expression (Abe et al., 2009). Shin et al. (2009) correlated the presence of catechin in green tea with its activity in reducing the risk of type 2 diabetes. Tan et al. (2008) isolated four cucubitanate glycosides and concluded that these compounds could be used as potential agents to treat diabetes and obesity. Khan and Anderson (2003) reported that its dried seed have insulin potentiating activity. In another study Hamid et al. (2008) reported that its methanolic extract have shown high insulinotropic activity among 14 tested plants. But Srinivasan and Karunadevi (2005) did not find any change in plasma insulin levels after administration of its aqueous seed extract on alloxan induced diabetic rats. This could be due to the variation in method used to obtain its aqueous extract. Ataman and Idu (2007) reported that on parenteral administration of _Momordica charantia_ leaf extract, its long-term use should be avoided as it may have hazardous effects on liver.

_Murraya koenigii_: Murraya koenigii is a herbal plant and sometimes also called spreading shrub when it grows up to 2.5 m. This plant is widely used in spices and condiments but leaves of this plant are used as flavoring agent and folk medicine for the treatment of various diseases (Tembhurne and Sakarkar, 2010). Insecticidal activity of its crude extract to _Sitophilus oryzae_ and _Tribolium castaneum_ is recently reported (Rani and Devanand, 2011). Aqueous extract of this plant showed
significant decrease in blood glucose levels in both diabetic and non-diabetic rabbits, in addition its extract also showed improvement in glucose tolerance (Kesar et al., 2005). Kesar et al. (2007) analyzed the aqueous leaves extract activity in severe diabetic rats and found it effective in bringing down the severity level of disease. Arulselvan and Subramanian (2008) analyzed the effect of ethanolic leaf extract of *Murraya koenigii* on streptozotocin induced diabetic rats. They observed restoration of altered enzymatic and non-enzymatic antioxidant activities in liver and serum glucose and insulin levels. Arulselvan et al. (2006) reported the insulin stimulatory activity of its extract in experimentally induced diabetic rats. It is thought that its protective effects on pancreatic β-cells and antioxidant activity are major factors that contribute towards its hypoglycemic activity (Arulselvan and Subramanian, 2007). Improvement in glucose tolerance, insulin stimulatory activity and protective effect on pancreatic β-cells all in combination contribute towards its anti-hyperglycemic activity.

*Ocimum sanctum*: *Ocimum sanctum* (Tulsi) is an aromatic herb having stem trailing along the ground with 3-folate leaves (Rahman et al., 2010). This plant is famous for its medicinal value and used for various purposes to deal infectious wounds, cancer, as an antioxidant, anti neoplastic and anti-tuberculosis (Raghavendra et al., 2006; Hemalatha et al., 2011; Misra et al., 2006; Islam et al., 2011; Farivar et al., 2006). Some studies have reported insecticidal, nematocidal and antimicrobial activity of its extract (Vinayagam et al., 2008; Bharadwaj and Sharma, 2007; Rahman et al., 2010; Mishra and Mishra, 2011). Its extract also showed some developmental effects on fish immunity (Pavaraj et al., 2011). Same effect was observed in chicken when treated with a herbal mixture containing *Ocimum sanctum* as one of its herbal ingredient (Oyagbemi et al., 2008). Grounded leaves of *Ocimum sanctum* (locally known as “Tulsi”) with *Ocimum album* is used by local people for treatment of diabetes (Ahmad et al., 2009). Alcoholic extract of its leaves significantly decreases the blood glucose levels of alloxaan induced diabetic rats (Vats et al., 2002). Hussain et al. (2001) found that aqueous extract of *Ocimum sanctum* successfully reduced the fasting blood glucose and improved the glucose tolerance in streptozotocin induced diabetic rats. Its leaf powder showed both hypolipidemic and antihyperglycemic effects when fed to diabetic rats for one-month period (Rai et al., 1997). On administration of *Ocimum sanctum* extract a decrease in plasma glucose was observed in addition to an increase in liver and kidney weight in streptozotocin induced diabetic rats (Vats et al., 2004).

Joshi et al. (2011) reported the presence of anthocyanins in aqueous ethanolic extract of *Ocimum sanctum* and these anthocyanins act as stimulant for beta-cells to secrete insulin (Jayaprakasam et al., 2005).

*Phyllanthus amarus*: *Phyllanthus amarus* is a widely distributed pantropical weed usually grows under moist and shady places. Its stem leaves and seeds are extensively used for medicinal purposes (Khan et al., 2011; Costa et al., 2006; Idu and Onyibe, 2007; Annamalai and Lakshmi, 2009; Joseph and Raj, 2011). This plant is used in Dir Kohistan valleys (NWFP) as a herbal medicine (Jan et al., 2009). Alkaloids, flavonoids, terpenoids, saponins, tanins, steroids and cardiac glycosides are the active phytochemicals of this plant (Banikole et al., 2011). Srividya and Periwal (1995) found that it has hypoglycemic effect on treated group of humans. This plant showed antidiabetic activity both in insulin dependent and non-insulin dependent diabetic rats (Bavara and Narasimhacharya, 2007). Mice treated with its aqueous and seed extracts showed a dose dependent decrease in plasma glucose, cholesterol and weights (Adeneye et al., 2006). Compounds inhibiting the activity of enzymes (α-glucosidase, α-amylase), that are involved in carbohydrate digestion are considered as potential anti-diabetic agents (Tadera et al., 2006). Ali et al. (2006) examined the α-amylase inhibitory activity of *Phyllanthus amarus* hexane extract and identified the mixture of oleanolic acid and ursolic acid as potential α-amylase inhibitory compounds. Oleanolic acid showed hypoglycemic effect along with increase in weight and serum insulin levels of streptozotocin induced diabetic rats (Dawe et al., 2007). Ursolic acid showed a preservative effect on pancreatic β-cells in experimentally induced type 1 diabetic mice, as a result there was increase in insulin levels, which ultimately resulted in the reduction in plasma glucose levels (Jang et al., 2009). Chattopadhyay et al. (2006) reported its regenerative effect on liver and in another study an increased insulin activity is also reported after the administration of its hydroalcoholic extract in partially hepatectomised albino rats (Chattopadhyay et al., 2007). Careful use of *P. amarus* has been recommended by Adedapo et al. (2005) as some of its fractions had toxic effect on rat serum. All these finding conclude that inhibition of α-amylase enzyme and protective effect on β-cells may be the potential mode of action of *Phyllanthus amarus* against diabetes.

*Seamcarpus anacardium*: This plant is known for its therapeutic and antimicrobial properties (Veena et al., 2006; Sharma et al., 2010). Ethanolic extract of dried nuts showed significant antihyperglycemic effect in normal
and experimentally diabetic rats (Kothai et al., 2005; Arul et al., 2004). Its nut milk extract showed hypoglycemic activity along with increase in body weight and serum insulin levels in streptozotocin induced diabetic rats (Jaya et al., 2010). Nut shells mainly contain biflavonoids and oil of nuts contains a mixture of phenolic compounds, oleic acid, linoleic acid, palmitic acid, stearic acid and arachidic acid (Majumdar et al., 2008; Aseervatham et al., 2011). A mixture of isomeric forms of linoleic acid (a constituent of kernel oil) has hypoglycemic effect due to their insulin stimulating activity (Ryder et al., 2001). Ascorbic acid (a phytochemical of its kernel oil) helps to reduce the arterial stiffness in type 2 diabetic patients (Mullan et al., 2002). Phytochemical linoleic acid could be responsible for its main antidiabetic activity and presence of ascorbic acid makes it suitable to deal with diabetes related complications.

*Silybum marianum*: *Silybum marianum* is a very old herbal remedy, now a days it is used as anticancer, antidiabetic, cardioprotective and for many other purposes (Tamayo and Diamond, 2007; Nobakht et al., 2011). Hepatoprotective effects of this plant are well reported (Hasanloo et al., 2005; Madini et al., 2008; Dehghan et al., 2010). Maghani et al. (2004) concluded that extract of aerial parts of *Silybum marianum* have antidiabetic effect on streptozotocin induced diabetic rats. Its extract was also found to be useful against diabetic nephropathy in streptozotocin diabetic rats (Vessal et al., 2010). Huseini et al. (2006) studied the effect of *Silybum marianum* seed extract on fifty one type 2 diabetic patients and recorded an overall improvement in glycemic profile of patients. The use of this plant may help in the reduction of diabetes related complications.

*Trigonella foenum-graecum*: *Trigonella foenum-graecum* L. (locally known as Maithi) is a leafy vegetable widely grown in NWFP Pakistan (Marwat et al., 2009). Many authors have reported antimicrobial, anti-inflammatory, antioxidant, antihyperlipidemic and other beneficial medicinal activities of its plant extract (Bonjar, 2004; Subhashini et al., 2011; Semalty et al., 2009; Mohamed and Metwally, 2009; Al-Sobayil, 2008; Semalty et al., 2010; Premanath et al., 2011; Bahram et al., 2005). Useful application of its seeds in poultry are also reported (Abbas, 2010). Seeds and leaves of this plant are used for medicinal purposes including diabetes. *Trigonella foenum graecum* seed powder successfully lowered the plasma glucose levels and brings the altered enzymatic levels to normal values in alloxan-induced diabetic rats (Raju et al., 2001). Fowden et al. (1973) reported the isolation of 4-Hydroxyisoleucine from the seeds of *Trigonella foenum-graecum*. This amino acid showed glucose dependent insulin secreting activity (Sauvagne et al., 1998). Broca et al. (2004) concluded that this amino acid could improve the insulin sensitivity. In type II diabetic rats this compound showed insulin stimulating effect on pancreatic beta cells (Broca et al., 1999). Its antioxidant antihyperlipidemic, insulin secretary activity and reported positive effect in type 2 diabetes prove its significant effects as an antidiabetic agent.

*Zingiber officinale*: *Zingiber officinale* is a perennial herb, having one meter long erect stem and possesses tuberous rhizomes that are used as a spice in cooking throughout the world. Ginger plant bears purple flowers and there are some essential oils present in it, which provides good aroma to the spice (Mali et al., 2009). Its local name is "Adrak" and grown on large scale in different parts of NWFP, it is used as herbal medicine to treat a range of diseases (Marwat et al., 2009; En et al., 2008; Akram et al., 2011). Antibacterial, antimicrobial, nephroprotective, antioxidant and hepatoprotective activity of its extract is well documented (Adebolu et al., 2007; Neogi et al., 2007; Patrick-Iwuanyanwu et al., 2007; Hariansyah et al., 2007; Prakash et al., 2008; Sunilson et al., 2009; Abeer Waggas, 2009; Lakshmi and Sudhakar, 2010). Extract of *Zingiber officinale* is also reported to have nematicidal and mosquitoecdial activity (Hassan et al., 2001; Dadji et al., 2011). It is also reported as beneficial component of poultry feed (Herawati, 2010). Volatile oils, tanins, alkaloids saponins and flavonoids are reported as its active phytochemicals (Hashemi et al., 2008). The juice of *Z. officinale* showed antioxidant action in alloxan induced diabetic rats (Asha et al., 2011). Raw ginger extract at the rate of 500 mg kg\(^{-1}\) in streptozotocin induced diabetic rats showed potential antihyperglycemic, hypocholesterolaemic and hypolipidemic activity (Al-Amin et al., 2006). Its juice significantly reduced the fasting glucose levels and increased the insulin levels in streptozotocin induced type I diabetic rats (Akhami et al., 2004). A compound named as 6-Gingerol is reported by Johji et al. (1988) as an active constituent of ginger. For the treatment of type 2 diabetes this (6)-gingerol is reported as a potential antidiabetic, lipid lowering and antioxidant agent (Singh et al., 2009). Adanlawo and Dairo (2007) reported that its extract have not shown and harmful effects on different parts of albino Wistar rats. So the presence of (6)-gingerol and its reported potential to treat the type I diabetes make it suitable for both type I and type II diabetes.
DISCUSSION AND CONCLUSION

There are many factors which are critical in the development of diabetes. Decline of antioxidant defense mechanism along with high levels of free radicals (formed as a result of glucose oxidation and nonenzymatic glycation of proteins) generate an oxidative stress on patient (Maritim et al., 2003). This oxidation stress lead to the damage of cellular organelles, enzymes, increased lipid peroxidation and development of insulin resistance. Some herbal plants (A. cepa, A. sativum, C. sativum, O. sanctum, T. foenum-graecum and Z. officinale) have been reported for their antioxidant properties. Use of antioxidants reduce the antioxidant stress and improve diabetes (Rahimi et al., 2005) therefore herbal plants (with antioxidant activities) could decrease the harmful effects of free radicals. Herbs and herbal drugs act through different ways to reverse the diabetic complications. For example Urtica dioica is useful for the treatment of diabetes and its affects through pancreatic and extra pancreatic pathways (Mehri et al., 2011). While Phlomis anisodonata control diabetes by increasing insulin level and combacting oxidative stress through activation of hepatic antioxidant enzymes (Sarkhail et al., 2007). In support of our results that most of studied herbs act through antioxidant mechanism is Hasani-Ranjbar et al. (2008) who have listed herbal medicines which are safe against obesity as reported in this study that most of studied herbs have antioxidant effects. There are about 70% of diabetic patients, which suffer with hypertension (Dodson, 2002). Hypertension increases the risk of retinopathy, nephropathy and peripheral vascular disease in diabetic patient (Sowers et al., 1998). Three herbs out of 19 are reported for their anti-hypertension activities which are A. cepa, A. sativum and C. roseus. Lipid profile is also important in diabetic patient as with successful serum lipid control the risk for cardiovascular complications can be reduced in diabetic patient (Deshpande et al., 2008). In type 1 diabetes inflammation have negative effect on beta-cells function and strengthen the immune system against beta-cell destruction (Eizirik et al., 2009). Inflammatory cytokines such as tumor necrosis factor (TNF)-α and Interleukin (IL)-1β and free radicals are believed to play key roles in destruction of pancreatic β cells while Silybum marianum seed extract reduce levels of inflammatory cytokines such as TNF-α and IL-1β and oxidative stress mediators (Malhi et al., 2009) O. sanctum and T. foenum-graecum both have antiinflammatory and antilipemic activity, these two herbs can be employed to overcome these complication in diabetic patients. Some herbs are reported to have protective or regenerative effect on insulin producing beta-cells or liver (A. vera, E. scaber, M. koemigii, O. sanctum, P. amarus, S. marianum, T. foenum-graecum and Z. officinale). These herbs can be employed for treatment of type 1 diabetes. S. marianum, M. charantia and C. inybus are reported for their specific antidiabetic activity in type 2 diabetes. P. amarus and Z. officinale are reported for antidiabetic activity in both type 1 and type 2 diabetes. Toxicity of herbal plants should be studied as toxic effects of some herbs (A. cepa, A. sativum, A. herba-alba, C. roseus, C. colocynthis, M. charantia) have been reported. So time and duration of dose should be chosen carefully to avoid any harmful effect of applied herb. On the basis of reviewed literature four herbs O. sanctum, Z. officinale, T. foenum-graecum and P. amarus were found to be most effective in dealing with diabetes and its related complication. Inclusion of these herbs in daily food routine may help to reduce the prevalence of disease Pakistan.

REFERENCES


