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

[1]Asia Karim, [1]Muhammad Nouman, [1]Saba Munir and [2]Saba Sattar
[1]Asian Network for Scientific Information, Faisalabad, Pakistan
[2]Directorate of Land Reclaimation Irrigation and Power Department, Lahore, Pakistan

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 modren medical facilities to every person is not possible. In addition to economic constrains, reported side effects of these modern drugs encouroged 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. Ninteen 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. Out of the ninteen herbs *O. sanctum, Z. officinale, T. foenum-graecum* and *P. amarus* were found to be the 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 Zimmet, 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 Pieris-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 (Lefebvre, 2005). In 2007, 246 million people world-wide suffered from diabetes and this number

Corresponding Author: Asia Karim, Asian Network for Scientific Information, Faisalabad, Pakistan

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 published in News of future at http://www.newsoffuture.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 diabetes 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, pervasiveness 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; Gantait *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 € 7, 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. Metaformin 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; Kahn *et al*., 2006; Singh *et al*., 2007). Glinides 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 characterisitics and phytochemistry of Herbs and Herbal Drugs used for treatement 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 glucosides 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 sulphoxide) 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 flashy 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 Lawal, 2008; Abera *et al*., 2011; Butkhup and Samappito, 2011; Masaadeh *et al*., 2006; Philip *et al*., 2009; Shokrzadeh and Ebadi, 2006; Hasan *et al*., 2005; Sukandar *et al*., 2010). It is locally know 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 (Olusanmi 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 sulphoxide) 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; Mmereole, 2011; Odo *et al*., 2010; Oparaeke and Kuhiep, 2006; Panesar and Shinde, 2011). Different type of anthraquinones, saccarides, 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 gibberellin-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. Pritam 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 santonin and stigmasterol from flowering branches of *Artemisia herba alba*. Santonin 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 (Jaleel *et al*., 2009). Its extract showed a considerable wound healing, anti-tumor, hypotensive and antifungal activity (Nagori and Solanki, 2011; Rana *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 streptozocin 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 Colorectal Carcinoma Cell Line (HCT 116) and observed a dose dependent cytotoxic effect.

***Cichorium intybu*s:** *Cichorium intybu*s have stalked leaves with more or less hairy stem and toothed scales (Rose, 1981). Its extract have shown antihepatotoxic, anti-ulcerogenic and antimicrobial properties (Hasan *et al*., 2007; Madani *et al*., 2008; Dulger 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 "Kasni") 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 (Milala *et al*., 2009; Mulinacci *et al*., 2001). Mulinacci *et al*. (2001) characterized the chicoric acid and chlorogenic acid

from its leaves. This chicoric acid is reported as a potential antidiabetic agent with both insulin sensitizing and secretary property (Tousch *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). Inulin (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-glucuronide, quercetin-3-O-β-D-glucuronide) has been reported as phytochemicals of this plant (Mulinacci *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).

***Citrullus colocynthis*:** Almost all parts of *Citrullus colocynthis* are used for various purposes in Pakistan (Memon *et al*., 2003). Antidiabetic, antifungal, antibacterial, hypolipidaemic and local anesthetic activity of different plant parts extracts have been reported in various studies (Gurudeeban *et al*., 2010; Boulenouar *et al*., 2009; Hadizadeh *et al*., 2009; Thirunavukkarasu *et al*., 2010; Daradka *et al*., 2007; Ramanathan *et al*., 2011). Its extract is also used for the synthesis of nanoparticles (Satyavani *et al*., 2011b). Extracts of different fruit parts were analyzed for their insulinotropic effects (Nmila *et al*., 2000). All of the tested extracts showed potential insulin secretary activity and authors concluded that the antidiabetic activity of fruit is due to the presence of different phytochemicals (β-pyrazol-1-ylalamine) in its seeds. To some extent aqueous seed extract was found to have positive effect on streptozotocin induced diabetic rats (Al-Ghaithi *et al*., 2004). Isolation of various phytochemicals (alkaloids, flavonoides, 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 glycosidic 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 *Citrullus 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; Wagensteen *et 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 (Aruna *et al*., 1999).

***Cucurbita máxima*:** *Cucurbita máxi*ma 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 consumes 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 (Aruna *et al*., 1999). A range of sterols (25(27)-dehydroporiferasterol, clerosterol, isofucosterol, 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 a known hypoglycemic agent (Panda *et al*., 2009). But Jamaluddin *et al*. (1994) observed no hypoglycaemic 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, 28Nor-22(R)Witha 2,6,23-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). Safiyeh *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 (Safiyeh *et al.*, 2007b). Phytochemicals of this herb are mainly categorized as flavonoids, alkaloids, minerals, phenolic petrosins, triterpenoids, saponins and phytosterols (Sandhu *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 know 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 glycation 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 hypoglyceamic effect on alloxan induced diabetic rats (Ataman *et al.*, 2006). In another study its fruit methanolic extract has shown dose dependent hypoglycemic and antihyperglycemic 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 (Fernandes *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. Harinantenaina *et al.* (2006) identified two triterpene (5β,19-epoxy-3β,25-dihydroxycucurbita-6,23(E)-diene and 3β,7β,25-trihydroxycucurbita-5,23(E)-dien-19-al) 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 Siriamornpun, 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 cucurbitane 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 insulinotrophic activity among 14 tested plants. But Srinivasan and Karundevi (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 (Kesari *et al*., 2005). Kesari *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-foliate leaves (Rahman *et al*., 2010). This plant is famous for its medicinal value and used for various purposes to deal infectious wounds, cancer, as a 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, nematicidal 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 alloxan 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 (Bankole *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 (Bavarva 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 antidiabetic 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 aicd 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 (Dawei *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 hydroalcholic 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.

***Semecarpus 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; Madani *et al*., 2008; Dehghan *et al*., 2010). Maghrani *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 palnt may help in the reduction of diabetes related complications.

Trigonella foenum-graecum: *Trigonella foenum-graecum* L. (localy 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 (Sauvaire *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 secreatary activity and reported positive effect in type 2 diabetes prove its sifnificant effects as an antidiabetic agent.

***Zingiber officinale*:** *Zingiber officinale* is a perennial herb, having one meter long erected 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 (Malu *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; Ene *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; Harliansyah *et al*., 2007; Prakash *et al*., 2008; Sumlson *et al*., 2009; Abeer Waggas, 2009; Lakshmi and Sudhakar, 2010). Extract of *Zingiber officinale* is also reported to have nematicidal and mosquitocidal 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 antidiabetic 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 (Akhani *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 antioxidnats 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 thorugh pancreatic and extra pancreatic pathways (Mehri *et al*., 2011).While *Phlomis anisodonta* control diabetes by increasing insulin level and combating 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 obesty 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 reduced levels of inflammatory cytokines such as TNF-α and IL-1β and oxidative stress mediators (Malihi *et al*., 2009) *O. sanctum* and *T. foenum-graecum* both have antiinflammatory and antilipidemic 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. koenigii, 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. intybus* 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.

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