ISSN No:-2456-2165

Influence of *Foeniculum vulgare* Mill in the Management of Hyperglycemia

Sania Zulifqar
The University of Faisalabad

Abstract:- Use of many traditional herbal and medicinal plants as therapeutic purposes have been observed to fight with the diseases associated with lifestyle such as diabetes. Hyperglycemia is a recognized risk factor for diabetes. Many herbs such as *Foeniculum vulgare* Mill usually distinguished as fennel seeds due to its anti-diabetic activities have therapeutic properties to lower the elevated blood glucose level. Fennel is an aromatic medicinal plant of the Mediterranean zone and a well-known to the Indian, Greek, Egyptian and Chinese civilization. Numerous researches point approaching its pharmacological activities that comprises of anti-bacterial activity, hypoglycemic activity, gastro-protective activity, anti-inflammatory activity, cyto-protective activity, anti-anxiety activity, anti-fungal activity, anti-oxidant activity, anti-tumor activity, estrogenic activity, mycobacterium activity, estrogenic activity, chemo-protective activity, anti-cancer activity, cardiovascular and lipid activity, memory-protective activity and hepato-defensive activity. Proximate composition showed that F. vulgare seed's moisture content, crude protein content and crude fat, crude fiber, Ash and Nitrogen Free Extract content were 6.34, 9.28 and 9.56, 18.31, 12.87, 43.64, respectively. Hyperglycemic patients were selected and divided evenly in three groups (G_0, G_1, and G_2). Groups were prescribed to use a calculated quantity of fennel seeds at doses once daily on empty stomach by varying proportions. It is vibrant with the treatment that with fennel seeds, there was a significant decline in the blood glucose levels in diabetic patients after 2 hours of fennel administration, therefore demonstrating a good short term anti-diabetic activity. Before fennel administration, the mean values exhibited as 313.5 ± 108.69 and 279.33 ± 96.24 for patients having 100mg per kg body weight and having 50mg of per kg body weight. After 2 hours, the blood glucose levels for treated individuals showed mean values of 262 ± 88.69 for individuals having 100mg per kg body weight and 246.5 ± 91.93 for individuals having 50mg per kg of body weight. And the mean values for control group showed as 272.16 ± 89.84 before and 330.5 ± 91.87 after 2 hours.

I. INTRODUCTION

In developed and developing nations diabetes mellitus is a most prevalent and common disorder. It is speedily increase in ratio around the world (Tiwari and Rao, 2002). Diabetes is a major health problem and also a leading cause of Coronary Artery Disease (Xiyan *et al.,* 2017). Diabetes appears when body is impotent to yield adequate insulin or utilize insulin efficiently (Kahn *et al.,* 2006). It results from impaired insulin action, secretion, or both (Lindberg *et al.,* 2004). Deficiency of insulin in the body proceeds to chronic hyperglycemia with agitations of protein, carbohydrate and fat metabolism (Bastaki, 2005). Beta cells of pancreas that produce insulin demolished, may be due to patients own immune system or other factors lead to the development of type 1 diabetes (Ylipaasto., 2004). Destruction of insulin producing beta cells when combined with other environmental factors in a patient susceptible to it and diet with other conditions combined to develop type 2 diabetes (Kahn et al., 2006). Diabetes reports for a heavy load of morbidity and mortality (Renders *et al*., 2001). The predominance of diabetes mellitus is assumed to increase from the present 382 million individuals to 471 million by 2035 (Guariguata et al., 2014).

Diabetes is abundant both to the society and the influenced person. Generally, people with diabetes have impoverished health and their health expenditures are higher than those without diabetes. It is an distressing situation that diabetes occurrence in young Asian people is higher than in white people (Meltzer *et al.,* 1998). Advanced approaches for the management of diabetes is to control the blood glucose level (Hollander, 2007).

Diabetes has classified into many types but major two types are type 1 and type 2 (Alberti et al., 1998). A number of complications are linked with diabetes. Diabetic ketoacidosis resulting since unusual elevated glucose level (hyperglycemia) and coma as an outcome of decline blood glucose level (hypoglycemia) are critical metabolic complications linked with mortality. The most disastrous outcome of the diabetes is it's prolong vascular complications. There is wide range of complications and due to the persistent increase of the level of blood glucose which leads to the damage and narrowing of blood vessels (Nouwen *et al.,* 2011).

Recent studies has found that diabetes or hyperglycemia is not only a benign condition but also results in morbidity or mortality in hospitals during aggressive treatment (Clement et al., 2004). Diabetes related complications can be reduced by strict control of

ISSN No:-2456-2165

blood pressure, blood glucose and cholesterol (Kuusisto et al., 1994; Pyorala et al., 1997). Structured care is required to achieve strict control (Griffin et al., 1998). To improve and manage diabetes in the community, many local and national programs have been developed (Beckles at al., 1998). Obesity and diabetes are related to each other as obesity is a major risk factor in developing diabetes in society (Harris et al., 1998). Not only obesity but many other conditions like high level of blood glucose level, insulin resistance can also lead to other complications like high blood pressure, high level of lipids and cardiovascular diseases (Norris et al., 2005).

Complications of diabetes are sorted as macro-vascular disease (due to the damage to the arteries) and micro-vascular diseases (due to the damage to small blood vessels). The leading macro-vascular complications encompass increased cardiovascular disease. Micro-vascular complication encompasses neuropathy (neural damage), nephropathy (kidney disease) and retinopathy (eye disease). Sexual dysfunction, depression and dementia are other chronic complications of diabetes (Forbes and Cooper, 2013). World health organization (WHO) has reported that in 1995, 150 million people had diabetes and the number will be doubled in 2025 (Bnouham et al., 2001). Past studies have shown that glucose level can prevent many of the micro and macro vascular complications in diabetic patients (Hollander, 2007). In the development of diabetes mellitus, genetics paly a very important role (Cooke and plotnick, 2008).

The use of surrogate medication has accelerated and influenced the attention of researchers from all over the world (Hunt *et al.,* 2000). Apart from medical practices, there are many alternative medications are used such as herbal treatments, physical remedies, dietary approaches or cognitive treatments (Ginsburg, 1990). In the health and treatment of the humans, plants have played a very important role (Kooti et al., 2014). Use of herbs as a treatment among diabetics is common. People using Qur'an readings mostly use medical herbs. 400 herbal remedies have been reported that are used by the diabetics worldwide (Al-Rowais, 2002). A wide range of herbal medicines are used to treatment diabetes. After the significant improvement in the management of diabetes through the drugs, look for the natural plants for its management also going on (Ahmed et al., 2009). It is also a crucial cause of kidney diseases and blindness in adults. Generally, the disease immobilizes people during their median years. People with diabetes expire in their immature age than those not influenced by it (Anonymous, 1995).

Synthetic drugs have more side effects than medicinal herbs because medicinal herbs have antioxidant properties that can reduce the toxicity of drugs (Samani et al., 2013; Kooti et al., 2014). Solutions of dried flowers, leaves, and the alone dried leaves, the crushed fresh shoot and the volatile oils are the most common forms used (Sheikh, 1982). Polyphenols present in 80 spices has anti-glycation properties important in the management of diabetes mellitus (Elosta et al., 2012).

In the few past years, there has been an expanding development of herbal medicine because of their reduced side effects and natural origin. Spices have been suggest to retain anti-oxidant (neutralize the effects of ROS), anti-glycant (restrain the formation of AGEs) and anti-inflammatory capabilities (Dearlove *et al.,* 2008). Around the world, 422000 flowering plants, moreover 5000 ones have been used for the treatment of different diseases. And one of them is fennel which is very effective (Abe *et al.,* 2013). Fennel is the aromatic herb of Mediterranean area, mostly used as spice and medicinal herb. Radical scavenging activity was found in the wild fennel and total flavored and phenolic content higher than the both medicinal and edible fennel (Bernath et al., 1996).

Fennel is the oldest plants of spice which is widely growing in arid and semi-arid and is world's one of the most dimension medicinal herb due to its economic and pharmacological usage. Foeniculum vulgare Mill is recognized as the 'sweet fennel' is an aromatic and herbal plant grown commonly in Bangladesh essentially because of its seeds that are utilized for both medicinal and culinary purpose (Barros *et al.,* 2009).

Fennel is an edible herb that is used as savory formulations, liqueurs, sauces, confectionary etc. (Guilled and Manzanons, 1996). Fennels can be consumed in salad and can be cooked as kitchen vegetables due to its distinctive and promoted aroma and flavor (Atta-Aly, 2001). Because to its antiulcer and antioxidant properties, it is widely used for the treatment of neurological disorders (Delaram et al., 2011).

Fennel plant belongs to the Plantae Kingdom. Belonging to the *Apiaceae* family, fennel is an ordinary aromatic plant of the Mediterranean area. And it is a well-known to the Indian, Greek, Egyptian and Chinese civilization (Charlsen *et al.,* 2010). Fennel has been used for many other purposes as food, pharmaceutical, cosmetic and healthcare industries (Jamshidi *et al.,* 2012). Increased interest in finding anti-oxidants naturally occurring for their uses in foods and herbal material to substitute synthetic antioxidants, those are restricted due to their side effects such as carcinogenicity (Zheng and Wang, 2001).

Due to the therapeutic effects and culinary use of fennel, it is largely exported in different countries for centuries (puelo, 1980). It is also used for a variety of complaints, especially for those of digestive system (Javadi et al., 2008). Seeds roots, leaves and powdered form can be used, but seeds are the most effective medically and are normally used (Grieve, 1984; Javadi *et al.,* 2008). The natural active ingredients present can cause biological balance in the body and prevent the accumulation of drugs in the body (Samani et al., 2015). The recreated interest in natural products rather than synthetic has gain the focused attention on the plants that are a source of flavoring compounds (Yaylayan, 1991).

ISSN No:-2456-2165

It resides in the carrot family of plants. Diversified parts have been accounted for their antioxidant properties (Hilmi *et al.,* 2014). The plant has been accounts to have the anti-diabetic, hepato-protective and anti-hyperlipidemic effects (Gengiah *et al.,* 2014). Fruits of the plant have been accounts to have analgesic, antioxidant and anti-inflammatory activities (Choi *et al.,* 2004). This herb also has antispasmodic, carminative, diuretic and analgesic effects and also used as a remedy for gastrointestinal disorders (Birdane *et al.,* 2007) (Dilaram *et al.,* 2011).

Seeds of this plant have potent to relieve pain during dysmenorrheal (Nejad *et al.,* 2006). Inhibit 5-lipoxygenase activity has been shown by the fruits and their constituents (Lee *et al.,* 2012). This medicinal plant is used widely for the treatment of diabetes. Leaves of this plant have been used for skin diseases (Kumar *et al.,* 2013). Aqueous extract of fennel seeds in dose-related manner, exhibits the hypotensive effects (Oktay *et al.,* 2003).

II. MATERIALS AND METHODS

The health giving worth of F. vulgare against hyperglycemia was investigated using bio valuation. Subjects from Madina teaching hospital Faisalabad were taken before starting the study. A recommended amount of F. vulgare powder in an empty stomach once in a day was prescribed to the chosen two groups. The amount of dose is mentioned below (Table 1).

Third group was control group. Blood sampling was carried out twice. First on the empty stomach in the morning to get the base values of all the humans' subjects and the next was carried out after 2 hours to evaluate the effect of the fennel seeds on the individuals. Proposed criteria contained a principle dominion namely blood glucose level.

Hyperglycemic, non-hypertensive and non-smoker males were chosen and divided into three groups.

Blood samples will be gathered 120 minutes after the dose administration and blood glucose level will be estimated by using their standard protocols.

By using the methods explained by Hossain *et al.,* 2014. Complete randomized Design was applied to find out the significance level. The statistical analysis of data was performed using two-way ANOVA and Tukey's HSD.

III. RESULTS

Determination of the proximate composition is significant role in screening of the raw material being used. Proximate analysis was performed on F. vulgare for varied quality, such as moisture, fat , ash and protein. Proximate composition exhibited that F. vulgare seed contains 6.34% was moisture content, 9.28% crude protein and 9.56% crude fat content. Crude fiber content, Ash, and Nitrogen Free Extract was as 18.31, 12.87, and 43.64, respectively in figure 1.

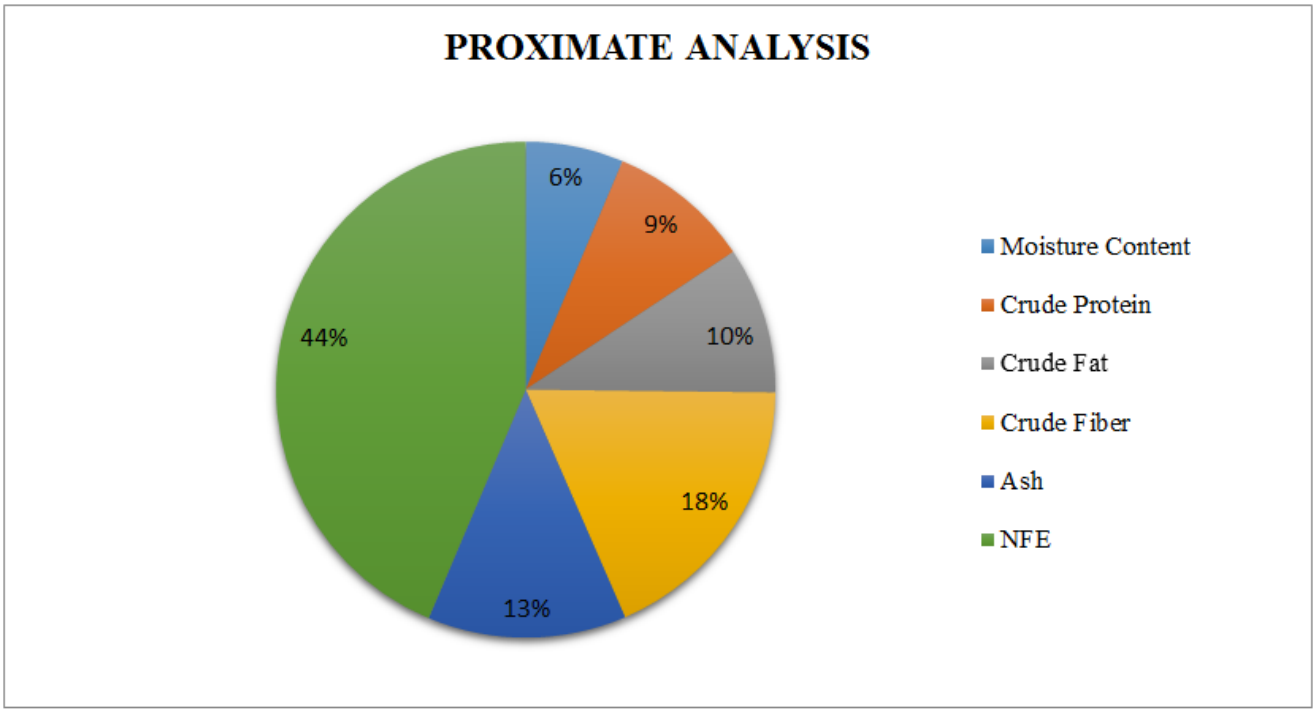

Fig 1:- Proximate Composition (%) of F. vulgare Seed Powder

ISSN No:-2456-2165

The activity of topically functional treatment on glucose tolerance is shown in table 1. In the current work, I've studied the anti-glycemic activity of fennel seeds. Fennel is one of the therapeutic herbs used for diabetes.

It is vibrant with the treatment that with fennel seeds, there was a significant decline in the blood glucose levels in diabetic patients after 2 hours of fennel administration, therefore demonstrating a good short term anti-diabetic activity. Before fennel administration, the mean values exhibited as 313.5 ± 108.69 and 279.33 ± 96.24 for patients having 100mg per kg body weight and having 50mg of per kg body weight. After 2 hours, the blood glucose levels for treated individuals showed mean values of 262 ± 88.69 for individuals having 100mg per kg body weight and 246.5 ± 91.93 for individuals having 50mg per kg of body weight. And the mean values for control group showed as 272.16 ± 89.84 before and 330.5 ± 91.87 after 2 hours. Fennel seeds have significant effects on the level of blood glucose of patients and could be used for hyperglycemia and this would offer high patient compliance and comfort.

Parameter	**Groups**	**Intervals Mean ± SD**	
Blood Glucose (mg/dL)		**0 hours**	**After 2 hours**
	G_0	258.54 ± 85.84	318.46 ± 91.87
	G_1	247.36 ± 91.93	220.55 ± 81.78
	G_2	363.00 ±93.97	302.73 ± 106.69

Table 1:- Means for Levels of Blood Glucose in Human Subjects Served with F. vulgare

G_0= Control group**; G_1=** Fennel seeds 50mg per kg body weight; **G_2 =** 100mg per kg body weight

IV. DISCUSSION

Use of fennel herb to treat diseases is a common practice since ancient times. Different parts of the plants are used in public health. Herbal medicines and natural remedies is a cost effective method used to treat diseases. According to the best of knowledge, in Pakistan, this type of study to explore the therapeutic potential of F. Vulgare seeds to attenuate hyperglycemia by using the human volunteers has not been yet conducted.

Fat, carbohydrate and protein each supply the total calories while ash and water only supply mass. The findings of present research regarding the proximate composition analysis of F. vulgare is in accordance with the ranges termed in the literature with the minor differences. Possible reasons behind the variations in the values could account to environmental factors such as location and climate of area. Furthermore, variations in the genetic makeup could also serve as a factor that contributes difference in the values.

According to Badgujar et al. (2014) stems and leaves show the highest content of moisture that is 77.46/100g and 76.36/g, respectively), while inflorescence contains the lowest content that is 71.31g/100g). In all the parts of fennel, carbohydrates are the most plenteous macronutrient range from 18.44 to 22.82g/100g. Proteins are the fewer plenteous macronutrient; proteins deviated between 1.37g/100g in the inflorescences and 1.08g/100g in the stems. The stems and inflorescences exposed the highest fat content that is 1.28g/100g and the reducing sugar content that is 1.49g/100g, respectively, among all the parts of the fennel. Reducing sugars are in small parts of carbohydrates because of the plenteous presence of cellulose which is a structural polysaccharide present as a component of the cell wall in plants and polysaccharides such as starch that is used majorly for the storage of energy in the plant cells. The highest content of ash was obtained from leaves that is 3.34g/100g, while the lowest level was present in stems that is 1.62g/100g. According to the proximate composition analysis, it can be estimated that a fresh new portion of 100g of these parts renounce, on average, 94kcal of energy. The highest values were investigated for inflorescences, while stems and leaves gave the lowest calorie contribution. Table summarizes the nutritional values and chemical proximate composition of different parts of the fennel plant, namely, leaves, roots, inflorescence, and stem.

Various medicinal schemes that have been disclosed as a natural medicine for hypoglycemia came from the efficacy of transmitted knowledge and have been used frequently in countries. Frequent herbal medicines are used traditionally for the treatment of diabetes mellitus. Aggravating manifestation in both clinical and experimental studies intimates that in the pathogenesis of diabetes oxidative stress plays a significant role (Hilmi et al., 2014).

Anti-hyperglycemic activity was ascertained through the oral glucose tolerance tests (OGTT). Administration of methanol extract of fennel seeds preceded to the important dose-dependent decline in the blood sugar levels in the sugar loaded mice. Different doses of 50, 100, 200 and 400 mg per kg of the body weight, the extracted dose-dependently declined blood glucose levels by 25.0, 42.4, 47.6, and 52.1%, reciprocally in contrast to the control animals. Correspondently, a measure of anti-hyperglycemic drug, when executed at a dosage of 10 mg per kg of the body weight, declined blood glucose level by 52.4%

occurs. Results showed that fennel seeds can be beneficial for the management of hyperglycemia (Monalisa and Rahmatullah, 2015).

V. CONCLUSION

F. vulgare was analyzed for varied quality attributes, such as moisture, fat and protein. On the basis of results of this research, it can be concluded that hypoglycemic effect of F. vulgare was significant. It has the ability to lower blood glucose level makes it ideal to use by diabetic patients. Fennel seeds have significant effects on the blood glucose levels of diabetic patients and could be used for hyperglycemia and this would offer high patient compliance and comfort.

REFERENCES

[1]. Al-Rowais, N. A. 2002. Herbal medicine in the treatment of diabetes mellitus. Saudi medical journal. 23:1327-1331.
[2]. Alberti, K. G. M. M., and P.F. Zimmet. 1998. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic Medicine. *15*:539-553.
[3]. Ahmad, M., R.Qureshi, M.Arshad, M.A.Khan, and M.Zafar. 2009. Traditional herbal remedies used for the treatment of diabetes from district Attock (Pakistan). Pak J Bot. 41:2777-2782.
[4]. Abed, K. F. 2007. Antimicrobial activity of essential oils of some medicinal plants from Saudi Arabia. Saudi Journal of Biological Sciences.14:53-60.
[5]. Barros, L., A.M.Carvalho, and I.C.Ferreira. 2010. The nutritional composition of fennel (Foeniculum vulgare): Shoots, leaves, stems and inflorescences. LWT-Food Science and Technology. 43:814-818.
[6]. Bastaki, A. 2005. Diabetes mellitus and its treatment. International journal of Diabetes and Metabolism. 13:111-120.
[7]. Barros, L., S.A.Heleno, A.M.Carvalho, & I.C.Ferreira. 2009. Systematic evaluation of the antioxidant potential of different parts of Foeniculum vulgare Mill. from Portugal. Food and Chemical Toxicology. 47:2458-2464.
[8]. Bernath, J., E.Nemeth, A.Kattaa, & E.Hethelyi. 1996. Morphological and chemical evaluation of fennel (Foeniculum vulgare Mill.) populations of different origin. Journal of essential oil research. 8:247-253.
[9]. Birdane, F. M., M.Cemek, Y.O.Birdane, I.Gülçin, & M.E.Büyükokuroğlu. 2007. Beneficial effects of Foeniculum vulgare on ethanol-induced acute gastric mucosal injury in rats. World Journal of Gastroenterology. 13:607-617.
[10]. Beckles, G. L., M.M.Engelgau, K.V.Narayan, W.H.Herman, R.E.Aubert, & D.F.Williamson. 1998. Population-based assessment of the level of care among adults with diabetes in the US. Diabetes care. 21:1432-1438.
[11]. Bnouham, M., A.Ziyyat, H.Mekhfi, A.Tahri, & A.Legssyer. 2006. Medicinal plants with potential antidiabetic activity-A review of ten years of herbal medicine research (1990-2000). International Journal of Diabetes and Metabolism.14:1-11.
[12]. Badgujar, S. B., V.V.Patel, & A.H.Bandivdekar. 2014. Foeniculum vulgare Mill: a review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. BioMed research international.
[13]. Choi, E. M., & J.K.Hwang. 2004. Antiinflammatory, analgesic and antioxidant activities of the fruit of Foeniculum vulgare. Fitoterapia. 75:557-565.
[14]. Clement, S., S.S.Braithwaite, M.F.Magee, A.Ahmann, E.P.Smith, R.G.Schafer, & I.B.Hirsch. 2004. Management of diabetes and hyperglycemia in hospitals. Diabetes care. 27:553-591.
[15]. Carlsen, M. H., B.L.Halvorsen, K.Holte, S.K.Bøhn, S.Dragland, L.Sampson, & I.Barikmo. 2010. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. Nutrition journal. 9;3-10.
[16]. Cooke, D. W., & L.Plotnick, L. 2008. Type 1 diabetes mellitus in pediatrics. Pediatr Rev. 29:374-384.
[17]. Delaram, M., Kheiri, S., & Hodjati, M. R. (2011). Comparing the effects of echinophora-platyloba, fennel and placebo on pre-menstrual syndrome. Journal of reproduction & infertility, 12(3), 221.
[18]. Dearlove, R. P., Greenspan, P., Hartle, D. K., Swanson, R. B., & Hargrove, J. L. (2008). Inhibition of protein glycation by extracts of culinary herbs and spices. Journal of medicinal food, 11(2), 275-281.
[19]. Elosta, A., T.Ghous, & N.Ahmed. 2012. Natural products as anti-glycation agents: possible therapeutic potential for diabetic complications. Current diabetes reviews. 8:92-108.
[20]. Forbes, J. M., & M.E.Cooper. 2013. Mechanisms of diabetic complications. Physiological reviews. 93:137-188.
[21]. Guariguata, L., D.R.Whiting, I.Hambleton, J.Beagley, U.Linnenkamp, & J.E.Shaw. 2014. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes research and clinical practice. 103:137-149.
[22]. Ginsburg, M. 1990. Complementary medicine. Practitioner. 234:1482-1499.
[23]. Grieve, 1 984. A Modem Herbal. Penguin, Not so modem (1930s?) but lots of information, mainly temperate plants. ISBN. 440-449.
[24]. Guillén, M. D., & M.J.Manzanos. 1996. A study of several parts of the plant Foeniculum vulgare as a source of compounds with industrial interest. Food research international. 29:85-88.

[25]. Griffin, S., & T.Greenhalgh. 1998. Diabetes care in general practice: meta-analysis of randomised control trialsCommentary: Meta-analysis is a blunt and potentially misleading instrument for analysing models of service delivery. Bmj. 317:390-396.
[26]. Harris, M. I., K.M.Flegal, C.C.Cowie, M.S.Eberhardt, D.E.Goldstein, R.R.Little, & D.D.Byrd-Holt. 1998. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults: the Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes care. 21:518-524.
[27]. Hilmi, Y., M.F.Abushama, H.Abdalgadir, A.Khalid, & H.Khalid. 2014. A study of antioxidant activity, enzymatic inhibition and in vitro toxicity of selected traditional sudanese plants with anti-diabetic potential. BMC complementary and alternative medicine. 14:149-160.
[28]. Hollander, P. 2007. Anti-diabetes and anti-obesity medications: effects on weight in people with diabetes. Diabetes Spectrum. 20:159-165.
[29]. Hunt, L. M., N.H.Arar, & L.L.Akana. 2000. Herbs, Prayer, and Insulin: Use of Medical and Alternative Treatments-One concern about the use of alternative therapies is the possibility that these therapies may be in. Journal of Family Practice. 49:216-223.
[30]. Javadi, S., M.Ilkhnipour, R.Heidari, & V.Nejati. 2008. The effect Foeniculum vulgare Mill (fennel) essential oil on blood glucose in rats. Plant Sci Res. 1:47-49.
[31]. Kahn, S. E., R.L.Hull, & K.M.Utzschneider. 2006. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 444:840-850.
[32]. Kuusisto, J., L.Mykkänen, K.Pyörälä, & M.Laakso. 1994. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. Diabetes. 43:960-967.
[33]. Kumar, R. B., & B.Suryanarayana. 2013. Ethnomedicinal recipes for skin and dermatitis & allied diseases from tribals of Sriharikota Island, Andhra Pradesh. Journal of Pharmacognosy and Phytochemistry. 2:1-15
[34]. Lee, J. H., D.U.Lee, Y.S.Kim, & H.P.Kim. 2012. 5-Lipoxygenase inhibition of the fructus of Foeniculum vulgare and its constituents. Biomolecules & therapeutics. 20:113-123.
[35]. Lindberg, G., U.Lindblad, & A.Melander. 2004. Sulfonylureas for treating type 2 diabetes mellitus. Cochrane Database Systemic Reviews. 3:254-265.
[36]. Meltzer, S., L.Leiter, D.Daneman, H.C.Gerstein, D.Lau, S.Ludwig, & D.Lillie. 1998. 1998 clinical practice guidelines for the management of diabetes in Canada. Canadian Medical Association Journal. 159:1-29.
[37]. Nouwen, A., G.Nefs, I.Caramlau, M.Connock, K.Winkley, & C.E.Lloyd. 2011. European Depression in Diabetes (EDID) Research Consortium: Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. Diabetes Care. 34:752-762.
[38]. Norris, S. L., X.Zhang, A.Avenell, E.Gregg, B.Bowman, C.H.Schmid, & J.Lau. 2005. Long-term effectiveness of weight-loss interventions in adults with pre-diabetes: a review. American journal of preventive medicine. 28:126-139.
[39]. Oktay, M., Gülçin, İ., & O.I.Küfrevioğlu. 2003. Determination of in vitro antioxidant activity of fennel (Foeniculum vulgare) seed extracts. LWT-Food Science and Technology. 36:263-271.
[40]. Puelo, M. A. 1980. Fennel and anise as estrogenic agent. Journal of Ethnopharmacology. 2:337-344.
[41]. Pyörälä, K., T.R.Pedersen, J.Kjekshus, O.Faergeman, A.G.Olsson, & G.Thorgeirsson. 1997. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes care. 20:614-620.
[42]. Renders, C. M., G.D.Valk, S.J.Griffin, E.H.Wagner, & W.J.Assendelft. 2001. Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systematic review. Diabetes care. 24:1821-1833.
[43]. Yaylayan, V. A. 1991. Flavor technology: recent trends and future perspectives. Canadian Institute of Food Science and Technology Journal. 24:2-5.
[44]. Ylipaasto, P., K.Klingel, A.M.Lindberg, T.Otonkoski, R.Kandolf, T.Hovi, & M.Roivainen. 2004. Enterovirus infection in human pancreatic islet cells, islet tropism in vivo and receptor involvement in cultured islet beta cells. Diabetologia. 47:225-239.
[45]. Zheng, W., & S.Y.Wang. 2001. Antioxidant activity and phenolic compounds in selected herbs. Journal of agricultural and food chemistry. 49:5165-5170.