Effect of Myrrh Extract (Mirazid®) on Experimentally Diabetic Rats

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ABSTRACT
Background: Diabetes is a metabolic disorder characterized by resistance to the action of insulin, insufficient insulin secretion or both. The major clinical manifestation of the diabetic state is hyperglycemia. However, insulin deficiency and/or insulin resistance also are associated with disturbances in lipid and protein metabolism. Myrrh (from the stem of the *Commiphora molmol* tree) is an oleo gum resin that may prove efficacious for the treatment of fascioliasis. The effect of myrrh on diabetes treatment is still unknown, therefore this study aimed to showing the effect of myrrh extract on diabetic rats. **Materials and Methods:** A total of 100 Albino rats were equally divided to 5 groups [control (G_1), diabetic (G_2), mirazid (G_3), co-treated diabetic rats with amaryl (G_4) and co-treated diabetic rats with mirazid (G_5)]. Induction of Type II DM was carried out by intraperitoneal injection of 65 mg kg^{-1} b.wt. of streptozotocin. Many biochemical and physiological parameters were determined as changes in body weight gain percent, oral glucose tolerance test, insulin, insulin sensitivity percent, Liver glycogen content, fructosamine, liver and kidney functions. Also, total protein and total antioxidant capacity in serum, liver and in kidney homogenate in different groups under study were detected. **Results:** Myrrh extracts have hypoglycemic activity through decreasing blood glucose level, enhancing insulin secretion, increasing liver glycogen content and decreasing serum fructosamine. Myrrh extracts have antioxidant activity through increasing total antioxidant activity of serum and tissues, increasing total protein in tissues and enhancing liver enzyme AST and kidney function. **Conclusion:** This study concluded that Myrrh extracts have hypoglycemic activity and antioxidant activity through decreasing total antioxidant activity.

Key words: Diabetes, myrrh, hypoglycemic activity, antioxidant activity liver, rats

INTRODUCTION

Diabetes is a metabolic disorder characterized by resistance to the action of insulin, insufficient insulin secretion or both (Atkinson and Eisenbarth, 2001). The major clinical manifestation of the diabetic state is hyperglycemia. However, insulin deficiency or insulin resistance also are associated with disturbances in lipid and protein metabolism. The vast majority of diabetic patients are classified into one of two broad categories; type 1 diabetes which is caused by an absolute deficiency of insulin and type 2 diabetes which is characterized by the presence of insulin resistance with an inadequate compensatory increase in insulin secretion (Van Tilburg *et al.*, 2001). Finally, there are a variety of uncommon and diverse types of diabetes which are

caused by infections, drugs, endocrinopathies, pancreatic destruction and genetic defects (Schnedl *et al.*, 1994).

Myrrh is oleo-gum-resins that obtained from species of the genus *Commiphora* comprising some species spread throughout tropical Africa and Asia (Tucker, 1986). Myrrh occurs in irregular tears or masses weighing up to 250 g with a reddish-brown or reddish-yellow colour, fragrant scent and aromatic, bitter and acrid taste (Thulin, 2000).

Myrrh consists of water-soluble gum, alcohol-soluble resins and volatile oil. Myrrh contains 7-17% of volatile oil, 25-40% of resin, 57-61% of gum together with some 3-4% impurities. The gum contains polysaccharides and proteins while the volatile oil is composed of terpenes, sesquiterpenes, esters, cinnamaldehyde, cuminaldehyde steroids, sterols and eugenol among other ingredients (Mincione and Iavarone, 1972). The presence of eugenol is of particular

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note because this is also an active ingredient of clove oil used for its local anaesthetic action in treating toothache (Ishii *et al.*, 1968). This gives credence to the use of myrrh in treating dental problems across many cultures. The sesquiterpene fraction contains furanosesquiterpenes (Tipton *et al.*, 2003). Myrrh's characteristic odor is derived from furanosesquiterpenes. Since antiquity myrrh has served as a constituent of incense, oil of myrrh is a valuable ingredient in perfumes (Yu *et al.*, 1993).

In a recent clinical trial in Egypt a purified extract of myrrh was used to treat patients with schistosomiasis at a dose of 10 mg kg^{-1} b.wt. for three days, with a cure rate of 91.7%. Side effects were limited to a low incidence of giddiness, somnolence and fatigue (Sheir *et al.*, 2001). On the basis of these results a pharmaceutical company in Egypt began marketing the drug in gelatin capsule form, naming it "mirazid". Each capsule contains 300 mg of purified commiphora extract and the package insert claims amelioration of all symptoms in one week (Ma *et al.*, 1992). Mirazid has been reportedly, widely prescribed by Egyptian private physicians, especially in rural areas. However, independent clinical trials since carried out in Egypt have reported low cure rates, it appears difficult to reproduce the original published claims for mirazid both in humans and in multi-centre *in vivo* studies. On the basis of these results, this unstandardised herbal remedy (the active ingredients of which have yet to be identified) cannot be recommended for the treatment of schistosomiasis (Ford *et al.*, 1992; Tousson *et al.*, 2013). Concern has also been expressed because the use of an ineffective agent prevents the individual from using proven effective drugs such as praziquantel. This has potential repercussions for the national schistosomiasis eradication programme which had dramatically reduced the serious morbidity due to the disease in Egypt by 2001 (Tipton *et al.*, 2003). The effect of myrrh on diabetes treatment is still unknown, therefore this study aimed to showing the effect of myrrh extract on diabetic rats.

MATERIALS AND METHODS

The experiments were performed on 100 male albino rats weighing 150±10 g and of 10-12 week's age. They were obtained from our laboratory farms, Zoology Department, Faculty of Science, Tanta University, Egypt. The rats were kept in the laboratory for one week before the experimental work and maintained on a standard rodent diet (20% casein, 15% corn oil, 55% corn starch, 5% salt mixture and 5% vitaminzed starch; Egyptian Company of Oils and Soap Kafr-Elzayat Egypt) and water available *ad libitum*. The temperature in the animal room was maintained at 23±2°C with a relative humidity of 55±5%. Light was on a 12:12 h light dark cycle. The experimental protocol was approved by Local Ethics Committee and Animals Research. All animals were weighed at the beginning and at the end of the study. The rats were randomly and equally divided into five groups (20 animals each).

Group I (G₁): This group was control group in which animals did not received any treatment

Group II (G₂): This group was induced for type II DM and considered as the diabetic control group

Group III (G₃): This group was treated with mirazid at a dose of 25 mg kg^{-1} b.wt. orally by gastric intubation for 30 days

Group IV (G₄): This group was induced for type II DM which were co-treated with antidiabetic drug glimiperide (amaryl®) at a dose of 2 mg kg^{-1} b.wt. (Van der Wal *et al.*, 1997) orally by gastric intubation for 30 days

Group V (G₅): This group was induced for type II DM and co-treated with mirazid at a dose 25 mg kg^{-1} b.wt. orally by gastric intubation for 30 days

Induction of Type II DM was carried out by intraperitoneal injection of 65 mg kg^{-1} b.wt. of streptozotocin (STZ) (Sigma-Aldrich Chemical Co., USA), dissolved in 0.1 M citrate buffer pH 4.5. After 3 days blood glucose level was monitored and only rats with blood glucose level above 280 mg dL^{-1} were used in the present study according to Wang and Gleichmann (1998).

Oral glucose tolerance test (OGTT): OGTT test was performed by leaving the rats fast for 8 h and then the blood was taken by a puncture of rat tail vein. Then the rats were given glucose by gastric intubation at a dose of 2 g kg^{-1} b.wt. The blood glucose concentration was measured again at 60, 120 min.

Glucose: The enzymatic colorimetric test for glucose by GOD-PAP method according to Rohlfing *et al.* (2002).

The radioimmunoassay of rat insulin utilizes ^{125}I-labeled insulin and a rat insulin antiserum to determine the level of rat insulin in serum, plasma or tissue culture media by the double antibody/PEG technique (Morgan and Lazarow, 1963). Homeostatic Model Assessment (HOMA) has been widely employed in clinical research to assess insulin sensitivity (McAuley *et al.*, 2001). Rather than using fasting insulin or a G/I ratio, the product of the fasting values of glucose

(expressed as mg dL^{-1}) and insulin (expressed as μU mL^{-1}) is divided by a constant: $I0 \times G0/405$. Liver glycogen estimation was done by analytical method as described by Seifter *et al.* (1950) that depends on the formation of a green color by the reaction of the sugars with anthrone reagent under acidic conditions. Determination of serum fructosamine according to Schleicher and Vogt (1990). The FRAP (Ferric reducing antioxidant power assay) procedures described by Benzie and Strain (1999). Total protein was determined according to Weichselbaum (1946). Kinetic method for the determination of Alanine aminotransferase (ALT) activity according to the recommendation of the Expert Panel of the IFCC (International Federation of Clinical Chemistry), without pyridoxalphosphate activation according to Reitman and Frankel (1957). Kinetic method for the determination of Aspartate aminotransferase (AST) activity according to the recommendation of the Expert Panel of the IFCC (International Federation of Clinical Chemistry), without pyridoxalphosphate activation (Reitman and Frankel, 1957). The enzymatic determination of urea (modified bert holt reaction) procedures described by Patton and Crouch (1977). The photometric colorimetric test for kinetic measurements of creatinine procedures described by Bartels (1971).

Statistical analysis: Data were expressed as Mean values±SE and statistical analysis was performed using one-way analysis of variance (ANOVA) and Tukey HSD test to assess significant differences among treatment groups. The criterion for statistical significance was set at $p<0.05$. All statistical analyses were performed using SPSS statistical version 16 software package (SPSS® Inc., USA).

RESULTS

There was statistically significant difference in body weight gain percent between G_1 and all groups, there was insignificant difference in body weight gain percent between G_2, G_4 and G_5, also there was significant difference in body weight gain percent between G_3 and all groups (Table 1). Table 1 showed that there was statistically significant difference in fasting blood sugar between all groups. There was statistically significant difference in 1 h blood sugar between G_1 and G_2, G_4, G_5 but there was insignificant difference in 1 hour blood sugar between G_1 and G_3. Also there was statistically significant difference in 2 h blood sugar between G_1 and G_2, G_4, G_5 but there was insignificant difference in 2 h blood sugar between G_1 and G_3. Table 2 showed that there was statistically significant difference in serum insulin between G_1 and all groups, there was insignificant difference in serum insulin between G_4 and G_5. Also there was statistically significant difference in insulin sensitivity between G_1, G_2, G_4 and G_5, there was insignificant difference between G_1 and G_3, also there was insignificant difference between G_2, G_4 and G_5. There was statistically significant difference in liver glycogen content between G_1, G_2, G_4 and G_5 but there was insignificant difference between G_1 and G_3, also there was insignificant difference between G_2 and G_5 (Table 2).

Table 2 showed that there was statistically significant difference in serum fructosamine between G_1, G_2, G_4 and G_5 but there was insignificant difference between G_1 and G_3, also there was insignificant difference between G_4 and G_5. Table 3 showed that there was statistically significant difference in serum total antioxidant capacity between G_1, G_2, G_4 and G_5, but there was insignificant difference between G_1 and G_3 also there was insignificant difference between G_4 and G_5. Also there was statistically significant

Table 1: Changes in body weight gain percent and oral glucose tolerance test in different groups under study

Parameter	G1	G2	G3	G4	G5
Body weight gain (%)	33.384±1.477[a]	14.024±0.811[c]	23.096±1.398[b]	13.358±0.63[c]	15.916±1.544[c]
Oral glucose tolerance					
FBS (mg dL^{-1})	82.9±1.754[d]	285.8±4.192[a]	67.9±1.140[e]	146.8±2.632[c]	194.2±3.454[b]
1 h BS (mg dL^{-1})	174.6±3.152[d]	480.7±5.451[a]	167.5±2.062[d]	331.8±3.972[c]	392.9±7.616[b]
2 h BS (mg dL^{-1})	119.5±3.354[d]	367.9±5.630[a]	116.8±2.511[d]	234.3±3.621[c]	277.9±12.798[b]

Data is expressed as Mean±SE of 20 observations. Means in the same raw with different superscript are significantly different (p≤0.05), G1: Control group, G2: Diabetic group without treatment, G3: Mirazid group only, G4: Diabetic group treated with amaryl, G5: Diabetic group treated with Mirazid, FBS: Fasting blood sugar, 1 h BS: One hour blood sugar, 2 h BS: Two hours blood sugar

Table 2: Changes in insulin, insulin sensitivity percent, liver glycogen content and fructosamine in different group under study

Parameter	G1	G2	G3	G4	G5
Insulin (μIU mL^{-1})	24.86±0.849[b]	3.36±0.255[d]	29.23±0.613[a]	6.62±0.226[c]	6.15±0.073[c]
Insulin sensitivity	5.08±0.269[a]	2.37±0.169[b]	4.90±0.155[a]	2.39±0.099[b]	2.94±0.069[b]
Liver glycogen (μg g^{-1} tissue)	7.76±0.120[a]	2.29±0.096[c]	7.94±0.086[a]	2.92±0.057[b]	2.55±0.072[c]
Fructosamine (μmol L^{-1})	249.60±4.868[b]	462.40±9.326[a]	220.20±1.993[b]	354.50±14.227[c]	385.90±2.842[c]

Data are expressed as Mean±SE of 20 observations. Means in the same raw with different superscript are significantly different (p≤0.05). G1: Control group, G2: Diabetic group without treatment

Table 3: Changes in total antioxidant capacity in serum, liver, kidney homogenate and total protein in liver and kidney homogenate in different group under study

Parameter	G1	G2	G3	G4	G5
Total antioxidant capacity					
Serum (Fe^{+2} μmol L^{-1} tissue)	776±19.146[a]	475.9±4.39[d]	824.7±24.36[a]	582.1±3.92[c]	563.4±2.353[c]
Liver (Fe^{+2} μmol g^{-1} tissue)	450±9.702[b]	233±3.159[d]	492.3±9.26[a]	374.8±4.74[c]	352.9±6.151[c]
Kidney (Fe^{+2} μmol g^{-1} tissue)	596.5±18.27[a]	336.6±2.86[c]	640.6±17.9[a]	438.1±3.10[b]	428.8±1.879[b]
Total protein					
Liver (mg g^{-1} tissue)	1.32±0.018[b]	0.64±0.0047[d]	1.85±0.028[a]	1.003±0.012[c]	1.002±0.0073[c]
Kidney (mg g^{-1} tissue)	1.61±0.0284[b]	0.93±0.0123[c]	1.78±0.0246[a]	0.96±0.0049[c]	0.92±0.0035[c]

Data is expressed as Mean±SE of 20 observations. Means in the same raw with different superscript are significantly different (p≤0.05), G1: Control group, G2: Diabetic group without treatment, G3: Mirazid group only, G4: Diabetic group treated with amaryl, G5: Diabetic group treated with Mirazid

Table 4: Changes in liver enzymes (ALT and AST) activities and kidney functions (urea and creatinine) in serum of different group under study

Parameter	G1	G2	G3	G4	G5
Liver enzymes					
ALT (U L^{-1})	18.5±0.95[c]	31.5±0.95[a]	15.5±0.957[a]	24.8±0.611[b]	30.1±1.233[a]
AST (U L^{-1})	164.2±2.5[d]	202±1.50[a]	142.5±2.609[e]	180.1±1.197[c]	191.2±0.84[b]
Kidney functions					
Urea (mg dL^{-1})	37±0.47[b]	42.8±0.35[a]	30.9±0.795[c]	37.82±0.480[b]	38.58±0.305[b]
Creatinine (mg dL^{-1})	0.648±0.01[d]	0.95±0.01[a]	0.547±0.0087[e]	0.845±0.0096[b]	0.745±0.0096[c]

Data is expressed as Mean±SE of 20 observations. Means in the same raw with different superscript are significantly different (p≤0.05), G1: Control group, G2: Diabetic group without treatment, G3: Mirazid group only, G4: Diabetic group treated with amaryl, G5: Diabetic group treated with Mirazid, ALT: Alanine transaminase, AST: Aspartate transaminase

difference in liver total antioxidant capacity between G$_1$ and all other groups but there was insignificant difference between G$_4$ and G$_5$. There was statistically significant difference in kidney total antioxidant capacity between G$_1$, G$_2$, G$_4$ and G$_5$ but there was insignificant difference between G$_1$ and G$_3$ also there was insignificant difference between G$_4$ and G$_5$.

There was statistically significant difference in liver total protein between G$_1$ and all other groups but there was insignificant difference between G$_4$ and G$_5$ (Table 3). Also there was statistically significant difference in kidney total protein between G$_1$ and all other groups but there was insignificant difference between G$_2$, G$_4$ and G$_5$. There was statistically significant difference in serum liver enzyme alanine transaminase (ALT) between G$_1$, G$_2$, G$_4$ and G$_5$ but there was insignificant difference between G$_1$ and G$_3$, also there was insignificant difference between G$_2$ and G$_5$. There was statistically significant difference in serum liver enzyme aspartate transaminase (AST) between G$_1$ and all groups (Table 4).

There was statistically significant difference in blood urea between G$_1$, G$_2$ and G$_3$ but there was insignificant difference between G$_1$, G$_4$ and G$_5$. There was statistically significant difference in serum creatinine level between G$_1$ and all other groups (Table 4).

DISCUSSION

The present data showed that the body weight gain percent was significantly decreased after one month of intraprotoeneal injection of streptozotocin (G$_2$) in comparison with normal control group. Depression in body weight change may be explained that,

streptozotocin is a natural glucosamine-nitrosourea compound. As with other alkylating agents in the nitrosourea class, it is toxic to cells by causing damage to the DNA, though other mechanisms may also contribute. Schnedl et al. (1994) reported that, Streptozotocin is similar enough to glucose to be transported into the cell by the glucose transport protein GLUT2 but is not recognized by the other glucose transporters. The present results also, detected that; an increase in body weight gain in treated group with mirazid when compared with diabetic group with out treatment. Guyton and Hall (2000) find that, this treatment may be stimulate most aspects of carbohydrate metabolism, including rapid uptake of glucose by the cells, enhanced glycolysis, enhanced gluconeogenesis, increased rate of absorption from gastrointestinal tract and even increase insulin secretion with its resultant secondary effects on carbohydrate metabolism. Also the present data, showed insignificant difference in body weight gain percent between diabetic group without treatment (G$_2$), diabetic group co-treated with amaryl (G$_4$) and diabetic group co-treated with mirazid (G$_5$). This may be due to that the abnormalities of triglyceride storage and lipolysis in insulin-sensitive tissues such as the liver are an early manifestation of conditions characterized by insulin resistance and are detectable earlier than fasting hyperglycemia, also the body energy were obtained from lipids due to insulin deficiency and inability of the cells to assimilate glucose, thus elevation in blood glucose occurred and obtain energy from lipids which in turn lead to decrease in body weight. Our results agreed with Lewis et al. (2002).

The present results showed that mirazid decreased the fasting blood glucose level in the treated groups significantly when compared with the diabetic untreated group but still there was a significant increase when compared with the normal control group. This may be due to the hypoglycemic and hyperinulinemic activities of mirazid which may be attributed to its phytosterols which have a hormonal action or, to its polysaccharides content which have hypoglycemic activity in animals. Diabetic treated with amaryl, showed a significant decrease in the level of blood glucose due to the effect of amaryl through stimulating insulin secretion by interacting with specific receptors on the beta cell membrane by closure of ATP sensitive potassium channels with the resulting depolarization allowing influx of calcium ions into beta cells, thus trigerring the release of insulin containing secretory granules. Our results agreed with Lebovitz (1983).

The current results showed that there was significant increase in serum insulin level in normal and diabetic groups treated with mirazid when compared to diabetic control group. This may be due to hyperinsulinimic effect of myrrh as a stimulatory factor on the division of beta cells or contain non-metabolizable 2-deoxy and 3-O-methylglucoses which share the entry site, block the diabetogenic action of streptozotocin and restore insulin production and this agree with Shafrir (2003). Helal *et al.* (2005) reported that myrrh extract ameliorated the changes represented by increased number of islet cells. The present data showed that there was significant increase in serum insulin level in diabetic group treated with amaryl when compared to diabetic control group. This may be due to due to that sulfonylureas (amaryl) are insulin secretogogues, since they control blood glucose levels by directly stimulating first-phase insulin secretion in the pancreatic β cells.

Diabetes mellitus is known to impair the normal capacity of the liver to synthesize glycogen. Nomura *et al.* (2005) reported that the decreased in liver glycogen levels have also been reported in type II diabetic subjects and in some animal models of diabetes, thus suggesting impairment in glycogen syntheses activity. The current data agreed with Ferrer *et al.* (2003) who reported that the reduced insulin-stimulated glycogen synthesis is a characteristic finding in all insulin-resistant states, including diabetes. In the present study the liver glycogen content of the diabetic group without treatment, diabetic group treated with mirazid and diabetic group treated with amaryl was significantly decreased when compared to the normal control group which may be a result of increasing glucose output during insulin deficiency (Gold, 1970) and may be due to loss of glycogen synthetase activating system or increased activity of glucose-6-phosphatase

(Abdel-Moneim *et al.*, 2001). Also the liver glycogen content was slightly increased in the mirazid treated group than the diabetic group but not to the normal level of the control ones may be due to increased insulin level which has a potent effect on glycogen synthetase activity as well as on hepatic hexokinase and glycogen-6-phosphatase activity (Sheela and Augusti, 1992). The present results and Badian *et al.* (1994) results showed that there was a significant increase of liver glycogen content of diabetic group treated with amaryl when compared to diabetic group without treatment due to its lowering blood glucose which appears to be dependent on stimulating the release of insulin from functioning pancreatic β-cells.

Fructosamine concentration is a useful marker for the detection of persistent hyperglycemia and its differentiation from transient stress hyperglycemia. Also the measurement of fructosamine is an excellent tool for diagnosis and monitoring the treatment of diabetes mellitus and should become an essential part of the control of the course of diabetes mellitus in animals (Elliott *et al.*, 1999). The present data showed a statistically significant decrease in serum fructosamine when compared to diabetic control group and showed significant increase in serum fructosamine when compared to normal control group. The decrease may be due to decrease in blood glucose level over the past 3 weeks by the hypoglycemic and hyperinsulinemic actions of both mirazid and amaryl.

Oxidative stress is the main cause of diabetic complications, there is a direct proportion between oxidative stress and diabetes. The increase in total antioxidant capacity of both serum and in tissues (liver and kidney) of diabetic group treated with mirazid may be due to various phytonutrients are known to be good antioxidants and exert a protective effect against oxidative damage to macromolecules. Several mechanisms are involved by which the medicinal plants protect the health include (1) Limiting cell growth by enhancing cell to cell communication, (2) Causing cell to die (apoptosis), (3) Arresting cell cycle progression, (4) Altering steroidal hormone metabolism, (5) Enhancing immune response and (6) Up-regulating the activity of enzymes that detoxify carcinogens (Bomser *et al.*, 1996). Cao and Prior (1998) and Miller *et al.* (1998) who reported that the antioxidant can inhibit the propagation of free radicals reactions that may ultimately lead to the development of degenerative disease including cancers, cardiovascular disease, age-related muscular degeneration, neurologic disease and rheumatoid arthiritis.

Although a possible mechanism by which myrrh or its product inhibits the lipid peroxidation process was not fully discussed, several possibilities may be

considered rendering them potent antioxidants. One possible is myrrh's content of polyphenolic groups which induce protective effect against reactive oxygen species (Qureshi *et al.*, 1993). A second possible mechanism of lipid peroxidation inhibition is inhibition of eicosanoid generation and cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism which are potent modulators of lipid peroxidation and tumor promotion (Bond *et al.*, 1993). A third possible mechanism is, the antioxidant effect of myrrh and it's product may be to scavenging of peroxides and other radical oxygen species as did by natural protectors against lipid peroxidation such as retinol, ascorbic acid, tocopherol, glutathione and antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase which have the capacity to scavange reactive oxygen species and lipid free radicals. These results agreed with Burits and Bukar (2000). Total antioxidant capacity of serum and in liver and kidney tissues of diabetic group treated with amaryl were increased when compared to that of diabetic control group. This may be due to amaryl administration to some extent, cause a decrease in MDA level and increase in the activity of catalase, total thiol and glutathione levels. The normalization of hyperglycemia seems to be the basic mechanism responsible for these changes. Our results agreed with Low *et al.* (1997) suggested that an extra pancreatic activity it could involve an intensification of the trans membrane transport of glucose and an increase in the glycolysis activity. The decrease of the intensity of oxidative stress may also be connected with the suggested influence of amaryl on the number of insulin receptors. Under its influence an intensification of the synthesis of glycogen and lipogenesis were noted and it also decreased glucose level and prevented its auto oxidation. Glucose auto oxidation is considered to be a source of free radicals and as a result peroxides in diabetes.

The increase of tissues total protein of diabetic group that treated with mirazid than that of diabetic group without treatment may be due to that polyphenols such as flavonoids have been reported to exert a strong inhibitory effect on MPO activity, as evaluated by an MPO-inhibition assay (Shiba *et al.*, 2008). The increase in total protein of tissues (liver and kidney) of diabetic group treated with amaryl (G_4) when compared to diabetic control group may be due to the hypoglycemic and hyperinsulinemic effect of amaryl which in turn decreased the libration of the free radicals that damage the tissues proteins as discussed above via MPO, due to the fact that diabetes has oxidative stress effect (Low *et al.*, 1997). The liver helps maintain normal blood glucose concentration in the fasting and postprandial states. Loss of insulin effect on the liver leads to glycogenolysis and an increase in hepatic glucose production. Abnormalities

of triglyceride storage and lipolysis in insulin-sensitive tissues such as the liver are an early manifestation of conditions characterized by insulin resistance and are detectable earlier than fasting hyperglycemia.

O'Brien and Granner (1991) suggested that, the above theories all attribute elevated transaminitis to direct hepatocyte injury. It is also hypothesized that elevation in ALT, a gluconeogenic enzyme whose gene transcription is suppressed by insulin, could indicate impairment in insulin signaling rather than purely hepatocyte injury.

The present study showed that there was a significant increase in serum liver enzymes (ALT and AST) of diabetic group without treatment, diabetic group treated with mirazid and diabetic group treated with amaryl when compared to normal control group. Also there was insignificant decrease of serum ALT of normal group treated with mirazid when compared to normal control group. Also there was significant decrease in serum AST of normal group treated with mirazid when compared to normal control group. The present data showed that a significant decrease in serum liver enzymes of diabetic group co-treated with mirazid when compared to diabetic group without treatment. This may be due to the hypoglycemic, hyperinsulinemic and antioxidant scavenging influences of mirazid. Also our data showed that there was a significant decrease of diabetic group treated with amaryl when compared to that of diabetic group without treatment. This may be due to the hypoglycemic and hyperinsulimemic effect of amaryl.

It is clear that diabetes can lead to kidney disease but just why high blood sugars should damage the glomeruli is unclear (Steffes et al., 2010). The present data showed that there was a significant increase in Blood Urea Nitrogen (BUN) of diabetic group without treatment when compared to that of normal control group. Also there was insignificant increase of BUN of both diabetic group treated with mirazid and diabetic group treated with amaryl when compared to normal control group. Also there was a significant decrease in BUN of normal group treated with mirazid when compared to normal control group. When comparing blood urea nitrogen of diabetic group treated with mirazid with that of diabetic group without treatment we found that there decrease in that of diabetic group treated with mirazid. This may be due to the antioxidant, hypoglycemic and hyperisulinemic properties of mirazid.

The present data showed that there was a significant increase in serum creatinine level of diabetic group without treatment, diabetic group that co-treated with mirazid and that co-treated with amaryl when compared to normal control group. Also there was a significant decrease of serum creatinine level of normal group treated with mirazid when compared to normal control

group. There was a significant decrease of serum creatinine level of diabetic group treated with mirazid when compared to that of diabetic group without treatment. This may be due to hypoglycemic, hyperinsulinemic and antioxidant effects of mirazid. Also; there was a significant decrease of serum creatinine level and blood urea nitrogen of diabetic group treated with amaryl when compared to those of diabetic group without treatment. This may be due to hypoglycemic, hyperinsulinemic and antioxidant effects of amaryl.

CONCLUSION AND RECOMMENDATION

Myrrh extracts have hypoglycemic activity through decreasing blood glucose level, enhancing insulin secretion, increasing liver glycogen content and decreasing serum fructosamine. Myrrh extracts have antioxidant activity through increasing total antioxidant activity of serum and tissues, increasing total protein in tissues and enhancing liver enzyme AST and kidney function. We recommended for further studies on metabolic and other biochemical aspects on the effect of myrrh extracts on diabetes mellitus.

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