Hypolipidimic effect of some medicinal plants on diabetic rats

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Abstract:

Our aim was to evaluate the hypolipidimic effect of aqueous extract of a famous mixture used in Saudi Arabia folk medicine that consists of Nigella sativa, Commiphora myrrha, Boswellia carterii Birdw, Ferule assa-foetida and Aloe vera and also the extract of each plant alone on alloxan induced diabetic rats.

Material and Methods :-The present study was carried out on 80 adult male albino rats $(120 \pm 20 \text{ g.b.wt.})$, the rats were divided randomly into 8 groups, the first group served as control group, the second group as alloxan induced diabetic rats, the third group was diabetic rats treated with mixture of folk medicinal plant (0.01g /100 g b. wt.), the fourth group: diabetic rats treated with Nigella sativa (0.01g /100 g b. wt.), the fifth group: diabetic rats treated with Aloe vera (0.005g /100 g b. wt.), the sixth group: diabetic rats treated with Ferule assa-foetida (0.01 g /100 g b. wt.), the seventh: diabetic rats treated with Boswellia carterii Birdw (1ml/100 g b. wt.) and the eighth group: diabetic rats treated with Commiphora myrrha (0.01 g ml/100 g b. wt.)

Results :- Serum total lipid, serum total cholesterol, LDL–cholesterol, and triglyceride recorded significant increases in diabetic, Nigella sativa, Commiphora myrrha, Boswellia carterii birdw and Aloe vera treated group. While the mixture and Ferule assa-foetida treated group, showed insignificant changes in serum total lipid, triglyceride, serum total cholesterol and LDL–cholesterol. On other hand, the mixture treated group and Ferule assa-foetida treated group showed significant decreased in the previous parameters. The serum HDL–cholesterol was significantly reduced in diabetic group throughout the experimental periods, otherwise, all treated group revealed insignificant changes till the end of experiment when compare with undiabetic rats.

Conclusion: The aqueous extract of a mixture consists of Nigella sativa, Commiphora myrrha, Boswellia carterii Birdw, Ferule assa-foetida and Aloe vera are useful for improvement of the lipid profile of alloxan induced diabetic rats fram each plant alone.

Introduction:

Diabetes mellitus, a leading worldwide metabolic disorder, is characterized by hyperglycemia associated with impairment in insulin secretion and/or insulin action as well as alteration in intermediary metabolism of carbohydrate, protein and lipids. Several reports indicate that annual incidence rate of diabetes mellitus will increase in future worldwide, especially in the developing countries (King *et al.*, 1998 and Kameswara Rao *et al.*, 2003).

Lipid abnormalities occur most commonly in diabetes in type 2 diabetic subjects, even in those who have reasonable glycaemic control. The characteristic pattern of blood lipids in type 2 diabetes is called 'diabetic dyslipidaemia' and consists of elevated serum total and VLDL (very low-density lipoprotein) triglyceride, low HDL (high-density lipoprotein) cholesterol and essentially normal total and LDL (lowdensity lipoprtein) cholesterol concentrations. The distribution of LDL subfractions, however, is altered, with a predomination of small dense LDL particles (sometimes called the 'type B' pattern) which are strongly related to vascular disease in the general population. Dysipidaemia is also present in patients with impaired glucose tolerance. Diabetic dyslipidaemia is a component of the insulin resistance syndrome (syndrome X), i.e. central or truncal obesity, hypertension, glucose intolerance, accelerated atherosclerosis, dyslipidaemia and insulin resistance (Reaven, 1998).

In type 2 diabetes, epidemiological studies have shown that serum triglyceride and lowered HDL cholesterol are more strongly associated with coronary heart disease than are total and LDL cholesterol. This may be because of the association of dyslipiaemia with the insulin resistance syndrome. There is little clinical trial information of the effect of lipid lowering on coronary heart disease in diabetes, although a few trials have included a small number of type 2 patients (Evans, 2001).

In recent years much prominence has been given to the association of high levels of blood chol~sterol and plasma triglycerides with atherosclerosis and ischaemic heart disease. Treatment of hyperlipidaemia is preferably dietary accompanied by other natural regimes. Drug therapy is reserved for the more intractable conditions. Natural products having a beneficial action include nicotinic acid and those fish oils containing high quantities of ω -3-marine triglycerides (Shukla *et al.*, 1995b).

The black seed Nigella sativa (N. sativa) is a type of plant that belongs to the Ranunculaceae family. (1) It has been used as a herbal medicine. The effect of N. sativa on blood glucose levels in normal and diabetic animals seem to be conflicting. In 1992, El-Naggar and El-Deib, reported that oral administration of powdered N. sativa seeds for three weeks produced minimal insignificant reduction in blood glucose in normal and alloxan-induced diabetic rats. On the other hand, the intraperitoneal administration of volatile oil of N. sativa to fasting normal and alloxon-diabetic rabbits produced significant hypoglycemic effects (Al-Hader et al., 1993). A plant mixture containing N. sativa administered once daily at doses of 0.5-1.5 g/kg body weight for one month to normal and diabetic rats produced significant reductions in serum glucose level only in diabetic rats. Another plant mixture containing N. sativa was also reported to produce a significant hypoglycemic effect in alloxan-induced diabetic rats (El-Shabrawy and Nada, 1996). The

only study which has been done on humans reported a significant decrease in blood glucose level after one week of oral ingestion of N. sativa powder at a dose of 2 g/day.

Ferula assa-foetida, Family (Umbellifervae), Devil's drug is native to Iran, Afghanistan, and Pakistan. In the 7th century B. C., Charak Samita, a Hindu medical treatise, proclaimed assa-foetida the best remedy for clearing gas and bloating. The asafoetida's Oleo-gum-resin are the main parts used, where it contains 6.17% volatile oil, as well as resin and gum. The volatile disulfides, which have an oil contains expectorant action. The oil also settles the digestion. Assa-foetida is taken for bronchitis, bronchial asthma, who-ping cough and other chest problems. It also lowers blood pressure (Chevallier, 1996). Sulfur compounds in the oil may protect against fat-induced hyperlipidemia (Duke, 2002).

Boswellia carterii birdw (Olibanum or Frankincinse) Family (Burseraceae) has been used historically in the Ayurvedic medical system of India for various conditions, including arthritis and other inflammatory conditions. Hayashi (1998) confirmed that B. carterii contains actyl acetate and octanol as main constituents. It has been found that the composition of the volatile oil is dependent upon its geographic location. Somalia oils contained quite high levels of alpha-pinene (42%) and, interestingly, Turkish, Israeli and Egyptian oils contained very little, but were high in octylacetate (28.5-68.5%).

Commiphora myrrha (Myrrh) Family (Blirseraceae) is native to Northeastern Africa, especially Somalia. Myrrh is one of the oldest known medicines and was widely used by the ancient Egyptians. It is an excellent remedy for mouth and throat problems, with a drying, slightly bitter taste, and it also useful for skin problems, atherosclerosis, hemorrhoid, heptoses, high cholesterol, stomatosis, immunodepression and hyperglycemia. The myrrh's Gumresin-volatile oil are the main used parts, where it contains (30-60%) gum including polysaccliarides, resin(25-40%), acidic volatile oil (3-8%), heerabolene, eugenol and many furansesquiterpenes (Al-Awadi

& Gumaa, 1987, Chevallier, 1996 and Duke, 2002).

A water extract of a mixture of five plants that used by Kuwaiti diabetics was studied for identification of its active components (Al-Awadi and Shoukry, 1988). Only the extracts of myrrh and aloe gums effectively increased glucose tolerance in both normal and diabetic rats. The remaining components, gum Olibanum, Nigella saliva seeds and gum assa-foetida were without effect. the anti-diabetic action of the plants extract may, at least portly, be mediated through decreased hepatic gluconeogenesis (Al-Awadi, et al., 1991 and Helal, et al., 2005).

Material and Methods

A-Plant extract:

Folk medicine of famous Saudi methods for antidiabetic plant was used. These plants are Nigella sativa, Commiphora myrrha, Boswellia carterii Birdw, Ferule assa-foetida and Aloe vera, which are bought from market. These plants used as a mixture and each one were water extracted alone.

Preparation of the aqueous extract: <u>Mixture:</u>

The plants were grinned and 10 gm of each were mixed and boiled in 100 ml dist. water for 10 min and cooled in room temperature and filtered. The extract was given orally at dose 0.01 g / 100gm b.wt., the used dose is equal to the human therapeutic in Paget and barnes, 1964.

<u>Nigella sativa:</u>

The extraction of Nigella sativa was prepared by boiled 50 gm of plant in 200 ml dist. water for 10 min. After cooled in room temperature and filtrated stored it in refrigerator. The oral daily dosage used was 0.01 g / 100 gm b.wt.

Commiphora myrrha, Boswellia carterii Birdw, Ferule assa-foetida and Aloe vera.

Their aqueous extract was prepared by boiled 50 gm of each plant alone in 100 ml dist. water for 10 min. After cooled in room temperature, the each extract was filtered and stored in refrigerator. The dose used was 0.01 g / 100 gm b.wt. daily as oral dose, except Commiphora myrrha and Aloe vera used 0.005 g $/100~\mbox{gm}$ b.wt. daily as oral dose.

B-Animals and experimental design:

Eighty mature adult male albino rats weight 120±20 g. they are obtained from NAMRU medical center. Animals were housed under standard environmental conditions and fed on rodent diet and some vegetables and stayed for 2 weeks for adapted the place before began the experiment.

The animals were randomly divided into eight groups (10 animals / cage), seven of them are fasted over night and then injected with single subcutaneous dose of alloxan freshly prepared in a dose 120 mg/kg b. wt. dissolved in 0.5 ml acetate buffer (pH 5.5) as the methods of Malaisse (**1982**) and the last group served as control group. After 48 hr. of alloxan injection, blood glucose levels were measured to make sure rats be diabetic (level more than 250 mg/dl). Seven days late the diabetic rats were divided for treated with herbal medicine as: -

- **Group1**:(Control group), 10 rats were given subcutaneous saline solution (0.01 ml/ 100 gm b. wt).
- **Group2**: (Diabetic group), 10 rats were treated Alloxan (120 mg/kg b. wt).
- **Group3:**(Mixture plants treated group), 10 diabetic rats with Alloxan treated with (0.01g/100 gm. b. wt.) aqueous extract of mixture plants.
- **Group4**: (Nigella sativa treated group), 10 diabetic rats with Alloxan treated with (0.01g/100 gm. b. wt.) aqueous extract of Nigella sativa.
- **Group5**: (Aloe Vera treated group), 10 diabetic rats with Alloxan treated with (0.005g/100 gm. b. wt.) aqueous extract of Aloe Vera.
- **Group6**: (Ferule assa-foetida treated group), 10 diabetic rats with Alloxan treated with (0.01g/100 gm. b. wt.) aqueous extract of Ferule assa-foetida
- **Group7**: (Boswellia carterii Birdw treated group), 10 diabetic rats with Alloxan treated with (0.01g/100 gm. b. wt.) aqueous extract of Boswellia carterii Birdw.
- **Group8**: (Commiphora myrrha treated group), 10 diabetic rats with Alloxan

treated with (0.01g/100 gm. b. wt.) aqueous extract of Commiphora myrrha

After 30 days of treatment, 5 rats of each group were decapitated, while the other half of each group kept for 15 days more without any additional treatment for recovery. At the end of the experimental period the animals were killed by cervical dislocation and 5 ml of blood was collected and the serum was separated and stored at -20C° until needed for analysis the following parameters.

C-Biochemical assays

1- Determination of serum total lipids:

Serum total lipids concentration was determined according to the Knight *et al.* (1972).

2- Determination of serum triglycerides:

It was estimated according to the methods of McGowam (1983).

3- Determination of serum cholesterols:

Serum cholesterols level has been estimated according to Schettler and Nussel (1975).

- **4- Determination of serum HDLcholesterols:**It was estimated according to the methods of Warnick *et al.* (1983).
- **5- Determination of serum LDLcholesterols:**Serum LDL-cholesterols was estimated according to the methods of Demacker *et al.* (1983).

D- Statistical analysis of the data:

In the present work, the data are present in tables as (mean + standard error). The significance of difference between the means were calculated according to "t" test (Snadecor and cohran, 1976).

Results

Data in table (1&2) and illustrated in figure (1&2) represented the effect of normal, diabetic (with Alloxan,120 mg/kg b. wt) and treated diabetic rats with aqueous extract of medicinal herbal mixture consists of Nigella sativa, Commiphora myrrha, Boswellia carterii Birdw, Ferule assa-foetida and Aloe vera and also each plant alone on serum total lipids, triglycerides, cholesterols, HDL-cholesterols and LDL-cholesterol and recovery period (15 days without any treated).

Highly significant increases (p<0.01) in serum total lipids, triglycerides, choles-

terol and LDL-cholesterol were recorded in diabetic rat group (G2) as compared with the control group (G1), while the HDL-cholesterol level was highly significant decreases (p<0.01) during the experimental period.

After treated and recovery period, group treated with mixture of plants (G3) showed insignificant changes in serum total lipids, triglycerides, cholesterol, LDLcholesterol and HDL-cholesterol levels when compared with the control group (G1). Otherwise, highly significant decreases (p<0.01) were recorded when compared with diabetic group (G2) except HDLcholesterol levels which showed highly significant increases (p<0.01).

In Ferule assa-foetida treated group (G6), serum total lipids and triglycerides showed non significant change, while highly significant decreases (p<0.01) was observed in cholesterol and LDLcholesterol and highly significant increases (p<0.01) in HDL-cholesterol levels when compared with the control group (G1) during experimental period when compared with diabetic group (G2), highly significant decreases (p<0.01) was recorded in serum total lipids, triglycerides, cholesterol, LDLcholesterol levels after both treated and recovery periods with the exception of HDL-cholesterol levels, which recorded increases significant highly (p<0.01) throughout experimental period.

The other groups (G4, 5, 7&8), showed highly significant increases (p<0.01) in serum total lipids, triglycerides, cholesterol and LDL-cholesterol levels, when compared with the control group (G1). On the other hand, highly significant decreases (p<0.01) were observed when compared with the diabetic group (G2) during experimental period. While HDLcholesterol level recorded non-significant changes throughout experimental period. Otherwise, highly significant increases (p<0.01) was showed when compared with diabetic group (G2) during experiment period except Aloe vera (G) and Boswellia carterii Birdw groups (G) which showed changes after insignificant treatment periods and showed highly significant increases (p<0.01) after recovery periods.

Hypolipidimic effect of some medicinal plants......

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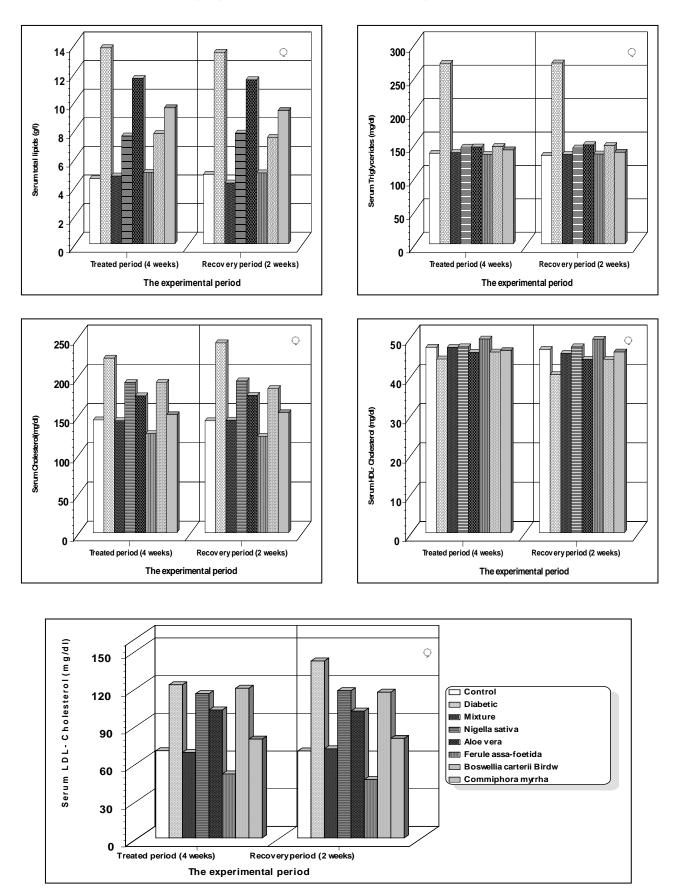


Fig. (1): Serum total lipids concentration (A), Triglycerides (B), Cholesterol level (C), HDL (D) and LDL (E) in control, diabetic and plant extracts treated male albino rats after 4 weeks of treatment and 2 weeks of recovery periods.

Discussion:

The present results elucidated that the rise in blood glucose was accompanied with marked increase in total lipids, triglycerides. total cholesterol and LDLcholesterol in diabetic rats. These data were confirmed with the results of Battell et al. (1998) and Abdel-Moneim et al. (2002) who declared that, marked elevation in serum triglycerides, cholesterol and LDLcholesterol levels in diabetic animals. This due to the decrease in lipoprotein lipase (LPL) activity secondary to insulin deficiency (Minnich and Zilversmit, 1989). Diabetic dislipidemia is due mainly to decreased removal of triglycerides into the fat depots and the increase in the plasma concentration of LDL-cholesterol (Tsutsumi et al., 1995).

The impairment of insulin secretion results in enhanced metabolism of lipids from the adipose tissue to the plasma (Briones *et al.*, 1984, Nikkila, 1984). In addition, leads to a variety of derangements in lipid metabolism, which inturn leads to accumulation of lipids such as total cholesterol and triglycerides in diabetic patients (Goldberg, 1981 and Shukla *et al.*, 1995a). However, Bopanna *et al.* (1997) reported that abnormal high concentration of serum lipids in the diabetic subject is due mainly to increase in the mobilization of free fatty acids from the peripheral fat depots.

The elevated level of serum triglycerides in diabetic animals of the present study may be as results of decreased clearance and increased production of the major transporters of endogenously synthesized triglycerides (Betteridge, 1986, Howord, 1987 & Rawi *et al.*, 1998).

The expansion of cholesterol pool in diabetes might be explained by (1) a higher input into system through an acceleration of intestinal cholesterol synthesis (Feingold *et al.*, 1985, O'Meara *et al.*, 1990 a and Mathe, 1995) or an increment of the rate of intestinal cholesterol absorption (Nervi *et al.*, 1974, Feingold *et al.*, 1985 and Mathe, 1995), (2) depression of the output due to decreased synthesis of bile salts (O'Meara et al., 1990) and/or by (3) diminished number of low density lipoproteins (LDL) receptors with consequent delayed clearance of cholesterol rich LDL particles (Mazzone et al., 1984).

On the other hand, LDL-cholesterol in serum of diabetic rats showed a significant increase. This abnormality certainly plays a role in the increased risk of cardiovascular disease. Increased LDL-cholesterol may be due to over production of vLDL by the liver or decreased removal of vLDL and LDL from the circulation (Tsustsumi *et al.*, 1995).

HDL-cholesterol concentration showed a very highly significant decrease after induction of diabetes by alloxan. These results go in agreement with the results of Lassko *et al.* (1986), Osman & Kandil (1991) and Punitha & Manoharan (2005) who reported, marked decrease of HDLcholesterol in serum of IDDM patients and alloxan diabetic rats. In contradiction to these results. On other hand, Rawi (1995) observed that very high significant increase of HDL-cholesterol in alloxan diabetic rats.

Otherwise. alloxan diabetic rats treated with the tested plants and their mixture extracts showed a decline in the total lipids as well as cholesterol and triglyceride levels when compared with diabetic rats. These observations indicate that the treatment with Nigella saliva, Aloe vera. Boswellia carteii Birdw and Commiphora myrrha partially ameliorated the toxic effects caused by alloxan. Otherwise, the treatment with Ferula assafoetida and the mixture ameliorated these toxic effects generally and turn back all lipids profile to normal values. This may be due to the correction of insulin level induced by these plants, which may cause a regulation of metabolism of carbohydrate and lipids by inhibitor of lipolysis. Since it inhibits the activity of the hormone sensitive lipases in adipose tissue and suppresses the release of free fatty acids stimulation of lipogenesis (Meral et al.,

2001, Gilani, 2004 and Ramalingam & Leelavinothan, 2005). While, the amelioration of serum cholesterol level may be due to stimulation of cholesterol excretion into the intestine, stimulation of the oxidation of cholesterol to bile salts, blocking the reabsorption of cholesterol from the gastrointestinal tract, preventing the reabsorption of bile salt and inhibition of cholesterol synthesis (Levy, 1977).

Cardiovascular diseases, including heart diseases and stroke, are leading cause of death in developed nations. In addition to hypertension, smoking and diabetes mellitus, elevated serum cholesterol is considered an independent risk factor for the development of coronary heart diseases (CHD) (Gorelick et al., 1999). Clinical trials of lipid-lowering agents in individuals without CHD (primary prevention) and in those with CHD (secondary prevention) reduction in cardiovascular reported mortality along with improvements in serum cholesterol levels (Shepherd et al., 1995, Sacks et al., 1996 and Dowas et al., 1998). Improvement management of dylipidemia has the potential to reduce the impact cholesterol plays in the development and squeal of cardiovascular diseases (Hoerger et al., 1999). The particular choice of lipid-lowering therapy in both primary and secondary prevention depends on the lipid profiles, the present reduction in LDLcholesterol needed, drug availability, adverse-effect profiles and medicinal costs (Brian et al., 2002).

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أظهرت الدراسة وجود زيادة إحصائية في الدهون الكلية والكوليستيرول والدهون ثلاثية الجليسرول في الجرذان المصابة بسكر الدم والمجموعات المصابة بسكر الدم وكذلك في التي تم معالجتها بكل من حبة البركة والصبر واللبان والمر على حدى بينما التي تم معالجتها بالمستخلص المائي للخليط أو بنبات الحلتيت فقد عادت إلى معدلاتها الطبيعية.

إما بالنسبة إلى HDL-cholesterol فقد انخفض انخفاضا ذو دلالة معنوية في مصل الدم المجموعة المصابة بسكر الدم ولم يتم معالجتها بينما كل المجموعات التي تم معالجتها فلم تظهر اى تغيير إذا ما قورنت بالمجموعة الضابطة

ولقد لوحظ من النتائج السابقة أن تأثير العلاج باستخدام المستخلص المائي للخليط أكثر فاعلية في تحسبين مستوى دهون مصل الدم من تأثير استخدام كل نبات على حدة (مما يدل على وجود تفاعلات لمكونات النباتات سويا) وهذا يحتاج الى در اسات أخرى .