Effect of some plant extracts on blood glucose and other biological parameters of type 2 diabetic patients.

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Abstract
Diabetes mellitus is a common chronic disease affecting millions of people worldwide. It characterized by chronic hyperglycemia due to relative or absolute lack of insulin or its actions. Traditional treatments are still limited to achieve the normal blood glucose in many patients. Searching for new, safe and effective hypoglycemic drugs or herbs for diabetic patients are needed. Therefore, the aim of this study was to investigate the aqueous extract of *Nigella sativa* seeds (black seed) and *Salvia officinalis* (Sage) as an adjuvant therapy in patients with diabetes mellitus type 2 in addition to their anti-diabetic medications. A total of 16 patients were divided randomly into two groups. Capsules containing dried aqueous extract *Nigella sativa* and *Salvia officinalis* were administered orally in a dose of 200 mg twice/day for ten days. Their effect on patients was assessed through measurement of fasting blood glucose (FBG), frequency of urination, Glutamic-Oxaloacetic Transaminase (GOT) and Glutamic-Pyruvic Transaminase (GPT) after 0, 5 and 10 days. Results showed that *Nigella sativa* caused significant reduction on FBG and urination after 5 and 10 days. Liver function including GOT and GPT showed also significant attenuation after 10 days. On the other hand, *Salvia officinalis* didn’t show significant effects on any parameters except of reduction on urination after 10 days. In Conclusion a dose of 400 mg/day of *Nigella sativa* might be a beneficial adjuvant as oral hypoglycemic agents in type 2 diabetic patients, moreover this dose did not adversely affect hepatic functions throughout the study period.

**Key words:** Diabetes, *Nigella sativa*, *Salvia officinalis*
تأثير بعض المستخلصات النباتية في تحسين مستوى جلوكوز الدم والقياسات البيولوجية الأخرى لدى مرضى السكر من النوع الثاني

المشتق:
مرض السكر هو مرض مزمن وشائع يصيب الملايين حول العالم. يتسم بارتفاع مزمن في سكر الدم مع نقص نسيبي لمستوى الأنسولين أو بقلة تأثيره. ولذا فإن العلاجات التقليدية عاجزة فيما عدا الأنسولين عن ضبط نسبة السكر في العديد من الحالات. لهذا نحن في حاجة ماسة للبحث عن أدوية أو أعشاب أكثر أمانا وفعالية. لذا فإن الهدف من هذه الدراسة هو دراسة تأثير المستخلصات النباتية لبذر حبة البركة وأوراق المرمرة عند إضافتها للنظام العلاجي لمرض السكر الغير معتمد على الأنسولين. وقد أجريت الدراسة على 16 مريضا تم قسمهم عشوائيا إلى مجموعتين وتم اعداد كيوليت تحتوي على المستخلص الماني لكل عشية على حدة تتكريز 200ملجم تؤخذ مرتين يوميا لمدة 10 أيام. تم تقييم الحالات عن طريق قياس مستوى السكر السمان في الدم وعد مرات النبولي ومستوى انزيمي الكبد بعد صفر، 5 و10 أيام.

أظهرت النتائج انخفاض معنوي واضحا في مستوى سكر الدم السمان وعد مرات النبولي بعد 5، 10 أيام من استخدام الحبة السوداء وانخفاض معنوي أيضا في مستوى انزيمي الكبد بعد 10 أيام فقط. على الجانب الآخر لم تظهر المرمرة أي تأثير معنوي على القياسات البيولوجية للمرضى الا انخفاض في عدد مرات النبولي بعد 10 أيام فقط. إجمالا فإن جرعة 400ملجم يوميا من الحبة السوداء ربما يكون لها تأثير إيجابي كعامل مساعد لأدوية النوع الثاني من السكر والأكثر من ذلك فإن هذه الدراسة لم تؤثر سلبًا على وظائف الكبد للمريض خلال فترة الدراسة.
**Introductions**

Diabetes is a chronic disease, occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. This leads to an increased concentration of glucose in the blood (hyperglycaemia). Globally, as of 2014, an estimated 387 million people have diabetes worldwide, with type 2 making up about 90% of the cases (IDF, 2014 and WHO, 2014).

Generally, diabetes is classified to two main types: type-1 diabetes (insulin-dependent diabetes mellitus) and type-2 diabetes (non-insulin-dependent diabetes mellitus). Patients with type 1 show a state of insulin deficiency because of severe defect in islet β-cell function while type 2 is characterized by a combination of resistance to action of insulin and insufficiency in insulin secretion (Ghorbani, 2013).

Currently, beside insulin, the most widely used medication for diabetes are oral hypoglycemic drugs including insulin sensitizers (biguanides, thiazolidinediones), insulin secretagogues (sulfonylureas, meglitinides), α-glucosidase inhibitors, incretin agonists and dipeptidyl peptidase-4 inhibitors (Lorenzati et al. 2010). The search for new antidiabetic agents with more effectiveness and less side effects has been continued. Medicinal plants have always been an important source for finding new remedies for human health problems. Traditionally, numerous herbs have been recommended for treatment of diabetes.

*Nigella sativa* L seed (also called black seed) is an annual herb of the Ranunculaceae family. It contains many active like nigellone, and thymoquinone, which was isolated from the volatile oil fraction (Padhyeet al. 2008). Three flavonoid glycosides and triterpenesaponins were also identified from *Nigella sativa* (Dadgar et al. 2006). Many studies showed that *Nigella sativa* improves glycemic control and ameliorates oxidative stress in patients with type 2 diabetes mellitus. placebo controlled participant blinded clinical trial, showed that long term supplementation with *Nigella sativa* improves glucose homeostasis and enhances antioxidant defense system in type 2 diabetic patients treated with oral hypoglycemic drugs (Kaatabi et al. 2015).

On the other hand, Salvia officinalis(also called sage) a one of the essential herbs with a savoury and slightly peppery flavor. Essential oil of sage contains cineole, borneol, and thujone. Sage leaf contains tannic acid, oleic acid, ursonic acid, ursolic acid, niacin, nicotinamide, flavones, flavonoid glycosides, corssole, corsnolic acid, fumaric acid, chlorogenic acid, caffeic acid, and estrogenic substances (Akhondzadehet al. 2003). Sage showed an improvement in glycemic control and lipid profile in hyperlipidemic type 2 diabetic patients consuming sage leaf extract randomized placebo. it may be safe and have anti-hyperglycemic and lipid profile improving effects in hyperlipidemic type 2 diabetic patients (Kianbakht and Dabaghian, 2013). Therefore the aim of this study was to investigate the aqueous extract of *Nigella sativa* seeds and *Salvia*
officinalis as an adjuvant therapy for patients with diabetes mellitus type 2, in addition to their anti-diabetic medications.

**Material and Methods**

**Herbs:**
Black seeds (*Nigella sativa* seeds) and sage leaf (*Salvia officinalis* leaf) were purchased as crude dried materials from local markets, Shbeen EL-Kom city, Monofya, Egypt. All samples were free of diseases and authenticated at faculty of pharmacology Tanta University.

**Kits:**
All diagnostic kits for blood glucose, Glutamic-Oxaloacetic Transaminase (GOT), Glutamic-Pyruvic Transaminase (GPT) were purchased from Bio diagnostic Co., Cairo, Egypt.

**Subjects:**
This study was carried out in 16 out patients of both gender (4 male and 12 female) at Sherbin central hospital, Mansoura, Egypt. The age of subjects ranged between 38-79 years old. All patients were suffered from diabetes type II (NIDDM). All the subjects signed a consent form before the start of study.

**Preparation of aqueous extract:**
Aqueous extract of two plant samples were prepared according to Elsaadany and Rawel (2008) with small modifications. Dried samples were cleaned using kitchen paper and grinded under cooling. A 50 g of each powder was soaked with 1 liter distilled water in conical flask over night at 4°C. Soaked samples were then heated in a water bath at 60°C for 6 hours. Samples were left to cool at room temperature and centrifuged at 5000 rpm then filtered using filter paper Whatman No.1. The filtrates were then dried at 45°C using vacuum oven. Each dried filtrates were capsulated at 200 mg with carboxyl methyl cellulose. All capsules were stored under cooling until use.

**Experimental design**
Sixteen patients divided randomly into two groups. Group 1 administered gelatin capsules containing 200 mg dried aqueous extract of *Nigella sativa* and carboxymethyl cellulose as filling material. Group 2: administered gelatin capsules containing 200 mg from aqueous extract of *Salvia officinalis* and carboxymethyl cellulose. Blood samples were collected from patient at the morning after overnight fasting at the 0, 5 and 10 days of administration. FBS, GOT and GPT were determined according to (Schumann *et al.* 2002) using ELITech Clinical Systems spectrophotometer at 340 nm.

**Statistical analysis:**
Data were represented as mean ± standard deviation, significance and differences between groups were statistically analyzed by (ANOVA) using Statistical Package of Social Science Program SPSS (version 21).
Results and discussion

Table (1): Effect of dried aqueous extract of black seed (*Nigella sativa*) and sage leaves (*Salvia officinalis*) on patients’ fasting blood sugar and urination frequency.

<table>
<thead>
<tr>
<th>Groups</th>
<th>FBS (mg/dl)</th>
<th>Urination frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 day</td>
<td>After 5 days</td>
</tr>
<tr>
<td>Black seed</td>
<td>188.3±56.3</td>
<td>161.0±23.5*</td>
</tr>
<tr>
<td>Sage</td>
<td>145.3±46.9</td>
<td>156.3±65.4</td>
</tr>
</tbody>
</table>

Data represented as Mean±SD of 8 replicates.
*(p≤ 0.05) between 0 day and other periods.

Figure (1): Effect of dried aqueous extract of black seed (*Nigella sativa*) and sage leaves (*Salvia officinalis*) on patients’ fasting blood sugar and urination frequency.

The effect of black seed and sage on fasting blood sugar and urination frequency are presented in Table (1) and figure (1). Results showed that *Nigella sativa* caused significant reduction on FBG and urination frequency after 5 and 10 days. On the other hand *Salvia officinalis* didn’t show significant effects on both parameters except of significant reduction on urination frequency after 10 days. These data was in agreement with *Hawsawiet et al. (2001)* that *N. sativa* seeds and their active ingredient, thymoquinone, have a promising reducing effect on the blood glucose levels in normal rats. Moreover, *Mohtashamiet al. (2011)* showed a significant decrease in fasting blood glucose and HbA1c levels in Black seed oil treated patients as compared to control group at the end of the study. On the other hand results of sage extract were not agreed with *Hajzadehet al. (2011)* that 4 hours after an injection of a sage waterextract, blood glucose decreased significantly in fasted normal mice and in fasted mildly alloxandiabetic mice, but not in fasted severely alloxan-diabetic mice.
Table (2): Effect of black seed and sage on liver function

<table>
<thead>
<tr>
<th>Groups</th>
<th>GOT (unit/l)</th>
<th>GPT (unit/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 day</td>
<td>After 5 days</td>
</tr>
<tr>
<td>Black seed</td>
<td>34.8±18.3</td>
<td>33.5±7.7</td>
</tr>
<tr>
<td>Sage</td>
<td>33.5±9.0</td>
<td>30.3±7.1</td>
</tr>
</tbody>
</table>

Data represented as Mean±SD of 8 replicates. *(p≤ 0.05) between 0 day and other periods.

Effects of black seed and sage on liver enzymes are presented in Table (2) and figure (2). As shown GOT and GPT are significantly reduced or attenuated to normal levels after 10 days by black seed. On the other hand, sage didn’t show significant effects after 5 or 10 days. These results also confirmed that both plants have no significant hazards on the liver. These results are in agreement with Kushwahet al. (2014) that black seed pretreatment significantly prevented the increase in liver enzymes and total bilirubin and decrease in GSH level in rats. On the other hand, Al-Khafaji (2014) showed a significant increase (p≤ 0.05) in GOT, GPT and total protein as compared with control occurred by black seed. Results of sage are agreement with Arabi et al. (2014) that plasma concentrations of protein, albumin and creatinine significantly increase where liver enzymes significant decrease.

The mechanism of the hypoglycemic effect of black seed has been suggested to be due to pancreatic actions via enhancing insulin secretion and inducing β-cell proliferation and regeneration (Kaatabi and Bamosa, 2015). Black seed may also improves systemic glucose homeostasis in diabetic by acting through increasing circulating insulin and enhancing the sensitivity of peripheral tissues.
to the hormone. They attributed this effect, in part, to an activation of the AMPK pathway in skeletal muscle and liver; and to an increased content of Glut4 in skeletal muscle (Bamosa and Kaatabi et al., 2015). In the present study, it was concluded that a dose of 400 mg/day of Nigella sativamight be a beneficial adjuvant as oral hypoglycemic agents in type 2 diabetic patients; moreover, this dose did not adversely affect hepatic functions throughout the study period.
References

