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# Effect of soybean seeds alone or in combination with insulin or glibenclamide on serum lipid profiles in alloxan-induced diabetic rats

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**Abstract**

The present study was conducted to evaluate the effect of soybean seeds administration alone or combined with either insulin or glibenclamide on serum lipid profiles in diabetic rats. Male Wister rats were induced diabetes by a single subcutaneous injection of alloxan 100 mg/kg.b.w.The rats randomly divided into six groups (eight rats in each group): The first group served as a control, the second group was administered soybean seed 400 mg/kg.b.w orally as suspension, the third group injected insulin 10 I.U/kg.b.w, subcutaneously, the fifth group administered glibenclamide 5 mg/kg.b.w. orally. Accompaniment of soybean seeds with either of insulin or glibenclamide given the fourth and sixth groups, using the same routes and doses in the individual groups. All treatments were once daily for two weeks. Soybean seeds treatment alone resulted in an improvement of body weight and decrease of triglyceride and total lipids levels. While treatment with insulin or glibenclamide as alone or combination with soybean seeds showed a significant reduction in the levels of total cholesterol, triglyceride, low density lipoprotein, and total lipids, beside a significant increase in both body weight and high density lipoprotein. Beneficial effects were seen when soybean seeds combined with either of insulin or glibenclamide treatment. These results indicate the usefulness of soybean seeds in the management of diabetes through the hypolipidemic effects of soybean seeds in diabetic rats.

***Keyword:*** Soybean, Diabetes, Alloxan, Insulin, Glinclamide, Lipid profile.
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# تأثير بذور فول الصويا لوحدها أو بالترافق مع الأنسولين أو الداؤنيل على مستويات شحوم الدم في الجرذان المصابة بداء السكر المحدث الالوكسان

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**الخلاصة**

صممت تجارب هذه الدراسة لتقييم تأثير بذور فول الصويا لوحدها أو بالترافق مع الأنسولين أو الداؤنيل في مستويات شحوم مصل الدم في الجرذان المصابة بداء السكر. استخدمت ذكور جرذان من نوع Wister التي استحدث بها داء السكر عن طريق حقنها بمادة الالوكسان تحت الجلد بجرعة ١٠٠ ملغم/كغم من وزن الجسم.قسمت الجرذان عشوائياً إلى ستة مجاميع (كل مجموعة ثمانية جرذان): المجموعة الأولى: تركت دون معاملة كمجموعة سيطرة, المجموعة الثانية: تم إعطائها بذور فول الصويا ٤٠٠ ملغم/كغم من وزن الجسم عن طريق الفم بشكل مُعلق, المجموعة الثالثة: حقنت تحت الجلد بالأنسولين ١٠ وحدة دولية/كغم من وزن الجسم, المجموعة الخامسة: أعُطيت الداؤنيل ٥ ملغم/كغم من وزن الجسم عن طريق الفم, الترافق بين بذور فول الصويا والأنسولين أو الداؤنيل أعُطي للمجموعة الرابعة والسادسة على الترتيب باستخدام نفس الطريقة والجُرعة المستخدمة في المعاملات الانفرادية. كل المعاملات كانت

لمرة واحدة باليوم ولمدة أسبوعان.أظهرت نتائج المعاملة الانفرادية ببذور فول الصويا تحسناً في وزن الجسم مع انخفاض في مستوى الكليسيريدات الثلاثية ومستوى الشحوم الكلية, بينما المعاملة الانفرادية لكل من الأنسولين والداؤنيل أو بالترافق مع بذور فول الصويا فقد أظهرت انخفاض معنوي في مستويات: الكولسترول, الكليسيريدات الثلاثية, الشحوم البروتينية ذات الكثافة الواطئة, والشحوم الكلية, إلى جانب زيادة معنوية في وزن الجسم ومستوى الشحوم البروتينية ذات الكثافة العالية. التأثير الأفضل لوحظ عند استخدام بذور فول الصويا بالترافق مع الأنسولين أو الداؤنيل. تشير نتائج الدراسة الحالية إلى أن بذور فول الصويا تمتلك دوراً في السيطرة على داء السكر من خلال التأثير المخفض لمستويات شحوم الدم في الجرذان المصابة بداء السكر.

## Introduction

Diabetes mellitus is a chronic metabolic disorder caused by insulin deficiency, often combined with insulin resistance, and it is a major cause of disability and hospitalization and it results in significant financial burden (1). WHO indicates that diabetes mellitus is one of the major killers of humans in our time (2).Management of diabetes without any side effect is still a challenge to the medical system,this has led to an increasing demand for natural products with antidiabetic activity and fewer side effects (3). Millions of people throughout the world consume soy products, in Asian countries; soybean has been stable for 5000 years (4). Soybean is unique foods because of their rich nutrient content, their complex carbohydrate and dietary fiber content contribute to their low glycemic indexes which benefit diabetic individuals and reduce the risk of developing diabetes (5). Previous study indicates that protein of soybean decreased cholesterol level in rats consume a diet rich in cholesterol (6). Soybean protein administration reduced cholesterol, triglyceride, and Low density lipoprotein levels in healthy persons (7) as well as in diabetic patients (8), similar effect was also noticed in rats (٩).The present study was designed to investigate the effect of soybean seeds alone or in combination with insulin or glibenclamide as hypolipidimic agent in experimentally diabetic rats.

## Materials and methods

Animals: Fifty six male albino rats, 3-4 months old and 167-218 gm body weight were housed in hanging cages and maintained under laboratory controlled of temperature (25 ±2) and light (14 hour light and 10 hour dark), pelleted food and tap water were given.

Induction of diabetes: Rats were fasted for 48 hour before inducing diabetes with alloxan (sigma chemical co., st, Lousis, Mo.USA). Diabetes was induced by a single subcutaneous injection of alloxan in a dose of 100 mg/kg of body weight (10). Rats were allowed to drink 5% glucose solution overnight to prevent drug induced hypoglycemia (11). Alloxan treated animals were monitored by periodic testing for glucosuria using Lilly Test Tap and ketonuria using chemstrip MH 5000/k (Boehrinher, Mannheim, Germany) for four weeks before treatments.

Experimental design: Soybean seeds were purchased from the local market in Mosul, and it's identify was confirmed biochemically in the Research Center of the college of Science, university of Mosul. The seeds were powdered before uses. After four weeks of induced diabetes the animals were divided into six groups each of 6-8 rats. Group 1: Diabetic control rats; Group 2: diabetic rats were treated with soybean seeds at a dose of 400 mg/kg.of body weight(12); Group 3: diabetic rats were treated subcutaneously with insulin (Actrapid, Novo Nordisk, Denmark) at a dose of 10 I.U. /kg of body weight (13); Group 5: diabetic rats were treated with glibenclamide (Medochemic LTD-Cyprus) at a dose of 5 mg tablet (5 mg /kg of body weight) (14), Group 4 and 6; diabetic rats were given soybean coadminstrated with insulin and glibenclamide, respectively at same routes and dose as in individual treatment. Soybean seeds and glibenclamide were given as a suspension orally by gavages needle. All treatment was once daily and lasted for two weeks.

Samples collection: Blood samples were collected from the orbital plexus of vein into clean dry centrifuge tubes allowed to clot, serum was separated after centrifugation at 1500 rpm for 15 minuets (15), serum lipid profiles were measured using colorimetric assay kits (Bicon, Diagnostic Gmbh, Burbach, Germany).

Statistical analysis: All data were analyzed by-one-way analysis of variance, the specific group differences were determined using Duncan multiple range test (16). The accepted level of significant was $P<0.05$.

## Results

Induced diabetes by alloxan lead after four weeks to a significant increase in levels of cholesterol, triglyceride, low density lipoprotein, and total lipids, with decreased significantly both body weight and high density lipoprotein (Table 1). Administration of soybean seeds as alone resulted in a significant increase in body weight with a reduction in levels of, triglyceride, low density lipoprotein in second week and total lipids in both two weeks (Table 2). When rats treated with insulin as alone or when companied with soybean seeds resulted a significant increase in body weight with a reduction in levels of low density lipoprotein, and total lipids in both two weeks, with significant reduction of levels of cholesterol, triglyceride

and increased level of high density lipoprotein in the second week only. Glibenclamide alone significantly increased body weight and high density lipoprotein levels in second week, while causes reduction in cholesterol, triglyceride, low density lipoprotein, and total lipids levels in both two weeks (Table 2).

Combination of soybean seeds with glibenclamide resulted an elevation of body weight with reduction of triglyceride level in the second week, and increase level of high density lipoprotein, with reduction levels of cholesterol, low density lipoprotein, and total lipids in both two weeks (Table 2).

Table 1: Comparison between normal and diabetic rats in body weight and lipid profiles.

| Parameters | Groups | | Normal Rats | Diabetic Rats |
|---|---|---|---|---|
| Body Weight (gm) | Before Treatment | | 201 ± 4.2 | 187 ± 4.5* |
| | After Treatment (weeks) | 1 | 204 ± 5.8 | 176 ± 5.3* |
| | | 2 | 217 ± 8.2 | 168 ± 5.8* |
| Serum Cholesterol level (mg/dl) | Before Treatment | | 77.2 ± 2.4 | 121.1 ± 3.4* |
| | After Treatment (weeks) | 1 | 78.4 ± 3.5 | 122.5 ± 5.5* |
| | | 2 | 77.0 ± 3.5 | 121.6 ± 5.1* |
| Serum Triglyceride level (mg/dl) | Before Treatment | | 58.8 ± 2.4 | 84.9 ± 4.3* |
| | After Treatment (weeks) | 1 | 58.5± 3.9 | 84.6 ± 3.8* |
| | | 2 | 59.9± 4.7 | 85.1 ± 3.2* |
| Serum HDL level (mg/dl) | Before Treatment | | 36.5 ± 2.4 | 69.8 ± 3.7* |
| | After Treatment (weeks) | 1 | 38.9 ± 2.7 | 72.6 ± 1.9* |
| | | 2 | 37.0 ± 3.1 | 74.5 ± 1.7* |
| Serum LDL level (mg/dl) | Before Treatment | | 28.9 ± 2.5 | 34.3 ± 4.1* |
| | After Treatment (weeks) | 1 | 26.7 ± 2.9 | 32.9 ± 1.4* |
| | | 2 | 28.0± 2.3 | 30.1 ± 3.3* |
| Serum Total lipids level (mg/dl) | Before Treatment | | 441 ± 12 | 863 ± 12* |
| | After Treatment (weeks) | 1 | 447 ± 12 | 875 ± 18* |
| | | 2 | 443 ± 12 | 871 ± 19* |

No. of rats (6-8) in each group, Data is the mean ± SEM, * Significant with normal rats at $P < 0.05$.

**Discussion**

In the present study, we have demonstrated that diabetes induced experimentally by alloxan produced significantly decreased in body weight, this result agrees with results of (17) in rats. The reduction of body weight in diabetic rats is due to dehydration and catabolism of fats and proteins (18), increased catabolic reaction leading to muscle wasting can be the cause of the reduced body weight gain in diabetic rats (19). Also the glucose can not enter the cells when there is lack of insulin lead to deficiency of energy for cells (20). Induced diabetes lead to increase level of cholesterol, (21) reported similar results in rats. The increase of cholesterol level occurs when there is an absence of insulin cause decrease level of Apo-mRNA (22), also deficiency of insulin lead to increase cholesterol- acyl- transferase that absorbs cholesterol from intestine, leading to increase level of cholesterol (23). Triglyceride levels also increased when diabetes induced by alloxan, this result agree with result of (24) in rats. This may be due to deficiency of insulin causing decrease activity of lipoprotein lipase that convert triglyceride to glycerol and fatty acids (25). Low density lipoprotein levels also increased, similar result reported by (26) in rats, this is due to increase synthesis from chylomicron and very low density lipoproteins (27).

Alloxan induced diabetes lead to increase levels of total lipids, this result agrees with result of (28) in rats, increase synthesis of very low density lipoproteins and chylomicron or decrease removal it from blood may be the causes of increase of total lipid levels (29).

Significant weight gain was observed in soybean treatment and these results are consistent with those of previous study (30) in mice, but our result not agree with result of (31) in rats. The possible mechanisms include, that soybean contain high percentage of protein, isoflavone, or fiber that increase metabolic processes in body (32).Insulin treatment showed an increase of body weight, similar observation has been reported in diabetic rats (33), but disagree with results of (34) in diabetic rats. This effect is due to its metabolic stimulatic effects that decrease lipolysis, increase fatty acid synthesis, increase amino acid uptake by the tissue, and increase protein synthesis (35) also insulin stimulate DNA replication, modulation of various enzyme activities, through increase translation of mRNA, and stimulate ribosome to produce protein (36), all this processes lead to improvement of body weight. Treatment with glibenclamide leads to improvement of body weight, (37) reported similar effects in diabetic rabbit, and this result disagree to result of (38) in type 2 diabetic patient.

Table 2: Effect of soybean seeds, insulin, and glibenclamide as alone and combination of soybean with either insulin, or glibenclamide on body weight, and serum lipid profiles.

| Groups | Weight Body g | | | Serum Cholesterol level (mg/dl) | | | SerumTriglyceride level (mg/dl) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before | After (weeks) | | Before | After (weeks) | | Before | After (weeks) | |
| | 0 | 1 | 2 | 0 | 1 | 2 | 0 | 1 | 2 |
| Control diabetic | E – F 187 ± 4 | FG 176 ±5 | G 168 ±5 | B – F 121.1± 3.4 | C –F 122.5 ±5 | C – F 121.6 ±5.1 | CD 84.9 ± 4.3 | CD 84.6 ± 3.8 | CD 85.1 ± 3.2 |
| Soybean seeds 400 mg/kg.b.w. | EFG 181 ± 4 | D – G 183 ± 7 | B – F 192 ± 4 | EF 124.6± 5.2 | B – F 120.4 ±6.6 | A – F 112.7 ±5.4 | BCD 79.9 ± 5 | BCD 80.9 ± 2.7 | AB 69.2 ± 2.8 |
| Insulin 10 I.U./Kg.b.w | A – E 195 ± 5 | A – E 198 ± 6 | ABC 202 ± 6 | EF 125.5± 2.4 | A – E 112.8 ±3.2 | A 102± 4.8 | CD 86.1 ± 2.4 | BC 75.3 ± 2.2 | A 56.6 ± 2.6 |
| Soybean seeds 400mg/kg.b.w + Insulin 10 I.U./Kg.b.w. | D – G 184 ± 4 | A – D 200 ± 6 | AB 208 ± 4 | B – F 121.1± 2.3 | ABC 109.3 ±1.9 | AB 107.7 ± 3.7 | BCD 81.7 ± 2.9 | BC 75.6 ± 2.4 | A 54.3 ± 4.5 |
| Glibenclamide 5mg/kg.b.w | D –G 184 ± 4 | C – F 189 ± 6 | B – F 192 ± 4 | DEF 123.5± 2.9 | AB 108.3 ±3.6 | A 106.5 ± 3.8 | D 91.1± 3.9 | BC 78.1 ± 4.7 | BC 71.5± 3.4 |
| Glibenclamide 5mg/kg.b.w + Soybean seeds 400 mg/kg.b.w | B – F 191 ± 5 | C – F 190± 5 | A 210± 4 | F 125.9± 2.6 | A – D 110.7 ±2.6 | A 105.3 ±3.7 | CD 83.5 ± 3.8 | BCD 80.5 ± 3.6 | B 74.3 ± 2.5 |

| Groups | Serum HDL level (mg/dl) | | | Serum LDL level (mg/dl) | | | Serum Total lipids level (mg/dl) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before | After (weeks) | | Before | After (weeks) | | Before | After (weeks) | |
| | 0 | 1 | 2 | 0 | 1 | 2 | 0 | 1 | 2 |
| Control diabetic | CDE 69.8 ± 3 | CDE 72.6 ± 1.9 | BCD 74.5± 1.7 | EFG 34.3 ± 4.1 | EF 32.9 ± 1.4 | DE 30.1 ± 3.3 | F 863 ± 12 | F 875 ± 18 | F 871 ± 19 |
| Soybean seeds 400 mg/kg.b.w . | DE 66.5 ± 2.8 | E 63.6 ± 3.2 | CDE 69.8 ± 2.9 | FG 42.1 ± 3.4 | FG 40.6 ± 2.4 | CD 25± 1.9 | F 856 ± 16 | E 796 ± 15 | D 701 ± 17 |
| Insulin 10 I.U./Kg.b.w | DE 67.4 ± 4 | CDE 72.4 ± 3.6 | AB 81.6 ± 3.2 | FG 40.9 ± 6 | BCD 22.3 ± 2.8 | AB 14 ± 0.5 | F 859 ± 17 | E 775 ± 16 | D 659± 11 |
| Soybean seeds 400mg/kg.b.w + Insulin 10 I.U./Kg.b.w . | CDE 68.2 ± 2.8 | ABC 77 ± 2.9 | AB 83.2 ± 2.1 | EFG 36.5 ± 3.1 | BC 20 ± 3.5 | A 4.9 ± 0.7 | F 867 ± 29 | D 604 ± 12 | A 382 ± 21 |
| Glibenclamide 5mg/kg.b.w | E 63.8 ± 2.5 | CDE 71.5 ± 3 | AB 80.5 ± 2.9 | G 43 ± 3 | BCD 21.1 ± 1.6 | A 9.7 ± 1.7 | F 854 ± 18 | E 788 ± 12 | E 776 ± 11 |
| Glibenclamide 5mg/kg.b.w + Soybean seeds 400 mg/kg.b.w | E 64.7 ± 3.3 | BCD 74.7 ± 1.8 | A 84.6 ± 2.5 | G 42.9 ± 4.6 | B 18.3 ± 3.1 | A 5.9 ± 0.8 | F 867 ± 16 | D 679 ± 12 | B 433 ± 13 |

No. of rats (6-8) in each group, Data is the mean ± SEM,
Different letters indicate significant differences between groups horizontally and vertically at $P < 0.05$.

Glibenclamide have an action like insulin so increasing the glucose translator and increase metabolism of it (39).

Earlier study has shown that cholesterol level was decreased in mice treated with soybean seeds by (40), and this has not confirmed in present study. Therefore, we believed that 15 days would not provide adequate exposure to have an effect. Treatment with insulin significantly decreased cholesterol level, previous studies by (41) in diabetic rats, showed same results. Alternatively, inhibition of acylcoenzyme of cholesterol acyl transferase in intestine that's absorbing cholesterol from intestine may play a role in observed lowering of serum cholesterol level (23), also insulin increase or stimulate synthesis of ApoE mRNA that leads to decrease level of cholesterol (42). Glibenclamide significantly decreased cholesterol levels, (43) reported similar result in type 2 diabetic patient, but not similar to result of (44) in type 2 diabetic patient, the glibenclamide reduce lipolysis that stimulated by isoproterenol lead to decrease liberate free fatty acids and cholesterol in blood (45), also decrease of free fatty acids leads to decease cholesterol level (46).

From the results soybean seeds reduced triglyceride level significantly, this result is in agreement with studies of (47) in diabetic rats, while (48) reported different result on postmenopausal women. Possible explanations for lowering triglyceride level include that soybean's content of isoflavones serve as a natural selective estrogen receptor modulator that exert an effect on lipid metabolism through their biological similarities to estrogen-receptor-dependent gene expressions. (49). or isoflavones affect in cellular lipid homeostasis by the down-regulation of sterol-regulatory-element-binding-protein (SREBP) and its target genes in the liver which are involved in the synthesis of triglyceride (50). Insulin treatment decreased triglyceride levels, a similar result reported by (36) in alloxan diabetic rats, insulin stimulate lipogenesis so increases level of triglyceride in fatty tissues and decreases its level in serum (51).Treatment with glibenclamide decrease triglyceride level, this result agree with (52) in type 2 diabetic patient, while (53) reported different result in type 2 diabetic patient. The reduction of triglyceride may be due to that glibenclamide is capable of exerting direct insulin like effect (54).

High density lipoprotein increased significantly in insulin treated rats; these result agreements with results of (55) in streptozotocin-induced diabetes rats, the insulin stimulate production and secret high density lipoprotein from intestine (56). Glibenclamide increase high density lipoprotein level, because it can act as insulin like effect as describe above.

Our study showed that rats treated with soybean resulted in reduction in low density lipoprotein levels; similar decreases was described previously in rats and hamster (57), our results disagreement with (58) in rabbit. This decrease duo to the fatty acids content of soybean increase activity of receptors of low density lipoproteins on adipose cells (25). Insulin treatment produced significant decrease in low density lipoprotein levels; similar observation was reported by (24) in diabetic rats. The increase number of receptors on monocyte cells by insulin leading to increase removal of low density lipoprotein from blood (59).Treatment of rats with glibenclamide produce a significant decrease of low density lipoprotein levels, also (55) reported similar results in type 2 diabetic patients, but disagreement with (60), in type 2 patient.

Total lipids levels decreased when rats treated with either of soybean, or insulin, or glibenclamide, as alone, This may be due to reduction in levels of cholesterol, triglyceride, low density lipoprotein, leading to decrease levels of total lipids because they are the total amount of lipids in blood at constant percentage (27).

When there are a combination treatment of soybean with either insulin or glibenclamide the improvement of body weight and increase of high density lipoprotein level, also reduction of cholesterol, triglyceride, low density lipoprotein and total lipids levels become better than rats treated with soybean, insulin, or glibenclamide as alone. This due to synergism of activity of soybean with activity of either insulin or glibenclamide.

The results of the present investigation clearly indicate that soybean seeds in a dose of 400 mg/kg of body weight found to be effective as antidiabetic through managing the complications associated with diabetes such as body weight maintenance and hyperlipidaemia, also our results suggested that combinations of soybean seeds with either insulin or glibenclamide increased antidiabetic activity

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