فعالية القيسوم المنجلي (القيسون)
في تدبير الداء السكري

وفيقة زرزور* ندى دهنة** دانية الاسطواني***
رغد سري**** رغد علاء الدين***** إيمان الحمصي******

الملخص

خلفية البحث وهدفه: يعدُّ الداء السكري من أكثر الأمراض انتشاراً في العالم، وتعتمد خافضات السكر الفموية والأنسولين في معالجته فضلاً عن المعالجة الشعبية. يلجأ بعض من مرضى الداء السكري في سورية إلى استعمال نباتات تنتمي إلى جنس الأخيلية كعلاجٍ موازٍ خافض لسكر الدم. هَدَفَتْ هذه الدراسة إلى تقييم دور القيسوم المنجلي (القيسون) بوصفه دواءً شعبياً واستخدامه خافضاً لسكر الدم.

مواد البحث وطرائقه: شارك في الدراسة 45 متطوعاً (19 ذكوراً، 26 إناثاً، بمتوسط عمر23.7 و22 سنة على الترتيب)، منهم 7 أفراد من دون قصة عائلية للداء السكري، 12 فرداً لهم أقرباء من الدرجة الأولى مصابين بالداء السكري، و26 فرداً لهم أقرباء من الدرجة الثانية مصابين بالداء السكري. أُجْرِيَ اختبار تحمل غلوكوز فموي (50غ) مرتين، إحداهما من دون تناول القيسون، والأخرى بعد تناول 70 مل من الخلاصة المائية للقيسون (بتركيز0.04غ/مل)، ثم حسبت المساحة تحت المنحنى لكلا الاختبارين. كما أُدْخِلَت الخلاصة المائية للنبات المذكور مرتين يومياً مدة أسبوع ضمن الخطة العلاجية لخمسة مرضى سكريين مع الحفاظ على جرعاتهم العلاجية المعتادة.

النتائج والاستنتاج: لم يلاحظ أي اختلاف في المساحة تحت المنحنى الأساسية عند كل من الإناث والذكور. كانت المساحة تحت المنحنى (2727.0 ±1355.3) بعد تناول الجرعة المحددة من القيسون أصغر بشكل ملحوظ (P=0.05) من المساحة تحت المنحنى الأساسية (3172.5 ± 1344.3) للمجموعة المدروسة. ظهر تأثير القيسون واضحاً في تخفيض المساحة تحت المنحنى لدى مجموعة المتطوعين من أقرباء الدرجة الأولى(P=0.03). كما انخفض مستوى الغلوكوز الصيامي عند اثنين من أصل خمسة من مرضى السكري. تبيّن الدراسة أنَّ من الممكن أن يكون للخلاصة المائية للقيسون تأثير خافض للسكر، مما يتوافق مع استخدامه في المعالجة الشعبية ولكن الأمر يحتاج إلى دراسات إضافية.

كلمات مفتاحية: القيسوم المنجلي (القيسون)، الأخيلية، داء السكري، اختبار تحمل السكر.

* رئيسة قسم الكيمياء الحيوية والأحياء الدقيقة– كلية الصيدلة – الجامعة العربية الدولية.
** قسم الكيمياء الحيوية والأحياء الدقيقة – كلية الصيدلة – الجامعة العربية الدولية.
*** كلية الصيدلة – الجامعة العربية الدولية.
**** كلية الصيدلة – الجامعة العربية الدولية.
***** كلية الصيدلة – الجامعة العربية الدولية.
****** كلية الصيدلة – الجامعة العربية الدولية.

The Efficacy of *Achillea Falcata* on Diabetes Mellitus Management

Zarzour W.[*] **Dehneh N.** [**] **Al Istwani D.**[***]

Serri R.[****] **Alaa eddin R.**[*****] **Homsi I.**[******]

Abstract

Background & Objective: Diabetes is one of the most common diseases. Many methods are used to manage the elevating blood glucose level, which varies between medications, insulin and traditional therapy. Many diabetic patients in Syria use Achillea Species and other herbal plants as part of their hypoglycemic therapy.

The present study evaluates the role of A.Falcata (A.F) as a traditional medicine and its efficacy in reducing blood glucose level.

Methods & Materials: Forty five Healthy volunteers participated in the study (19 male, 26 female, average age 23.7 and 22 years respectively).7 of them with no diabetic family history.12 had 1st degree diabetic relatives and 26 had 2nd degree diabetic relatives. Oral glucose tolerance test OGTT (50g glucose) was carried out twice; before and after administrating 70 ml of A.F aqueous extract (0.04g/mL), followed by the calculation of the incremental area under curve (IAUC) for both tests. Five diabetic patients used the extract twice a day for one week following herbalist recipe without interrupting their usual medication.

Results: No difference in basal IAUC was observed between female and male patients. IAUC after A.F use was (2727.0 ± 1355.3) significantly smaller than the basal IAUC (3172.5 ± 1344.3) in the studied group (p=0.05). Effect of A.F extract on reducing IAUC was obvious in the 1st degree group(p=0.03). Fasting blood glucose had diminished in two of five diabetic patients.

Conclusion: Our study demonstrates that the aqueous extract of Achillea falcata could have a hypoglycemic effect, which may support herbalist's traditional recipes. However, further investigations are needed.

Keywords: Achillea Falcata, diabetes mellitus, Oral Glucose Tolerance Test.

[*] Professor of Clinical Chemistry ، Faculty of pharmacy, Arab International University (AIU).
[**] Department of Biochemistry & Microbiology , Faculty of pharmacy, Arab International University (AIU).
[***] Graduates of faculty of pharmacy. Arab International University (AIU).
[****] Graduates of faculty of pharmacy. Arab International University (AIU).
[*****] Graduates of faculty of pharmacy. Arab International University (AIU).
[******] Graduates of faculty of pharmacy. Arab International University (AIU).

Introduction:

Diabetes is one of the most common diseases worldwide, which is spreading increasingly[1]. This disease may be life threatening, in 2012 diabetes was the direct cause of 1.5 million deaths[2]. Till now there's no absolute drug that can cure diabetes, patients use oral hypoglycemic drugs and Insulin injections in order to reduce blood glucose level. Despite using medications, some patients tend to consume traditional medicine to obtain a synergistic effect, such as *Artemisia, Rheum, Lupinus, Olea, Achillea and* the oil of bitter almond. *Achillea* genus is spread all over the world, with over than 140 species. The most common Syrian *Achillea* species are: *Achillea falcata (A.F) also known as A.damascena, Achillea fragrantissima* and *A. santolina*[3]. In general the genus is reported to have some hypoglycemic effect. According to that herbalists who gare the patients *A.F* claimed

it has the capability to reduce blood glucose level.

Literature illustrates that *A.santolina* had a high hypoglycaemic activity, which is mainly attributed to its antioxidant potential in streptozotocin (STZ) diabetic rats[4].

Investigation of antidiabetic activity of different *Achillea fragrantissima* extracts on STZ induced diabetic rats revealed that the aqueous extract decreases blood glucose by about 39%[5]. The infusions of *Achillea* species were tested on antioxidant enzyme systems of erythrocytes and *A.falcata* was the most effective one against catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD). There are some reports about the anti-proliferative activity of the isolated constituents from *A. falcata*[6-8]supported *A.F* use as a depurative agent and as an antimicrobial.

Some studies reported that *Achillea* species have flavonoids as an important part of their phytoconstituents[9]. Oran Kwon *et al*.(2007) suggested that flavonoids might have a hypoglycemic effect, by inhibiting some transporters like (GLUT2)[10] which is one of the transporter proteins that mediate the transfer of glucose and other sugars through the lipid bilayer in the intestine and in other tissues[11].

Information about *A.F* anti diabetic activity are lacking, in this study we investigate the effect of *A.F* on blood glucose response during glucose tolerance test (OGTT) in healthy volunteers. In addition, the response to *A.F* infusion was evaluated in diabetic patients.

Materials and methods:

- ***A.F* aqueous extract preparation:**

Previously dried *A.F* plant was collected from the herbalists' shops at Al Bzuriae region, in Damascus. 3 g of finely powdered dried aerial parts, were soaked in 70 mL hot water (not boiling) for about 10 minutes. Excessive heating may drive off the volatile oil.

- **Flavonoids detection**: Flavonoids were detected in the aqueous extraction using the general and characteristic reactions; Shinoda and Wilson Taubok[12,13].

- **Populations and study design:**

1- Healthy participants:

The sample consists of 45 healthy volunteers at the faculty of Pharmacy at Arab International University AIU; (19 male) with an average age of (23.7±3.5 years), and (26 female) with an average age of (22±1.38 years). Volunteer should not have acute or chronic illness and should not be on chronic medications.

Information about participant's age, gender, and family history concerning diabetes were obtained. Waist, hip-circumferences and height were measured to the nearest 0.5 cm, and weight was measured with a lever balance to the nearest 100 g. Body Mass Index (BMI) was calculated as weight in kg divided by the square of standing height in meters (m^2).

Regarding family history of diabetes, volunteers were divided into 3 groups:

- zero degree (0 dg) group: no family history of diabetes
- 1st dg group: mother or/and father with diabetes
- 2nd dg group: uncle or /and grandparents with diabetes.

Volunteers had undergone OGTT twice, with a week-time interval, the first test was performed to evaluate the participants' base line glucose tolerance, and the second was performed with administrating the *Achillea* dose. Capillary blood samples were collected for OGTT in capillary tubes containing heparin followed by centrifugation for 5 minutes on Hettich® centrifuge (Haematocrit 210). Plasma glucose was measured with glucose oxidase method using Sinnowa® Semi automatic Biochemistry analyzer BS-3000M.

-First OGTT was carried out as follows: All subjects received a 50 g glucose in 200ml water, following a 12-h overnight fast. This dose was chosen since diagnostic information obtained with 50 or 100g challenge at one and two hours does not differ[14]. OGTTs with four glucose measurements over two hours were recorded at 0 (fasting plasma glucose level FBG), 30, 60 and 120 min after glucose administration. These measurements were transformed

into OGTT glucose curves and a glucose tolerance base-line was obtained for the volunteers.

-The second OGTT: OGTT was initiated with the fasting plasma glucose level measurement, followed by *A.F* dose. 30 min later; 50g of glucose were administrated. OGTT was performed with the same measuring steps of the first OGTT (at 30 , 60 , 120 minutes).The four measurements of OGTT were also transformed into OGTT glucose curves.

2-Diabetic participants: Five diabetic patients (3 male and 2 female) were willing to use the plant extract in combination with their usual treatment(s). Extract was prepared as mentioned previously in this paper. It was used twice a day during a week: at night before sleeping and during the day before the main meal.

Fasting Blood Glucose (FBG) level was measured, using Codefree® glucometer, the day before starting extract administration and every morning during the trial.

Statistical analysis:

In this Observational study, data are presented as mean ± standard deviation. The incremental areas under the curve (IAUC) for plasma glucose concentrations during the OGTT were determined by the trapezoidal method. T-test was used to evaluate the presence of differences among pairs of samples; ($p \leq 0.05$) was considered significant.

Results

1-Results of flavonoid detection

General and characteristic reactions like: Wilson Taubock (detection of 5 or 3 hydroxy-flavonol and Flavon) demonstrated the presence of these compounds in the aqueous extract. Shinoda reaction, used for the detection of flavanones, was also positive.

2- Anthropometric parameters

45 healthy University students (19 male - 26 female) aged between (18 and 25 years) participated in this study. Demographic characteristics of the participants, which include age, Body mass index (BMI) and Waist to hip ratio (WHR) are shown in table (1). Male had significantly higher BMI and WHR than female.

Table (1): Demographic characteristics of participants. n (number),BMI (Body Mass Index),WHR (Waist to Hip Ratio).

	female	male	p
n	26	19	
Age	22±1.38	23.7±3.5	0.049
BMI	22.3±2.4	26.3±4.4	0.001
WHR	0.75±0.07	0.86±0.04	0.00009

3- OGTT results

IAUC for basal OGTT and OGTT after *Achillea* administration showed no statistically deference between male and female ($p>0.05$) (table 2)

Table (2): IAUC results in female and male volunteers before and after using A.F extract. IAUC (incremental Area Under the Curve)

	Female (mean ± SD)	Male (mean ± SD)	p
IAUC (basal)	3172.5±1344.3	3215.2±1433.4	0.92
IAUC (*Achillea*)	2727±1355.3	2544.4±1462	0.66

No correlations were observed between BMI or WHR and IAUC (basal or after *Achillea*) in the study group.

4-The role of diabetic family history

Table(3): IAUC results (mean±SD) before and after AF administration regarding diabetic family history. n (number), F (female), M (male),dg (degree), NS (not significant).

family history	n	Sex F/M	Basal IAUC	IAUC after AF	p
0 dg	7	6/1	1961±413	2179±1022	NS
1st dg	12	6/6	3776±1071	2579±1185	0.03
2nd dg	26	15/11	3081±1273	2713±1778	NS

Since the average of IAUC after *Achillea* administration (2727.0 ± 1355.3) was less important ($p=0.05$) than the average basal IAUC (3172.5 ± 1344.3) in the study group, volunteers were divided into three groups depending on their family history concerning diabetes. As it shown in (table 3), effect of *Achillea* on reducing IAUC was obvious in the 1st dg group ($p=0.03$). Basal IAUC in 1st dg group is significantly ($p=0.004$) significantly different from basal IAUC in 0 dg group. Noting that basal IAUC in 1st dg group is significantly larger than basal IAUC in 0 dg group.

5-Patterns of OGTT in response to *Achillea*:

Several patterns of OGTT in response to *Achillea* administration were observed in our study (figures 1a, 1b, 1c, 1d).

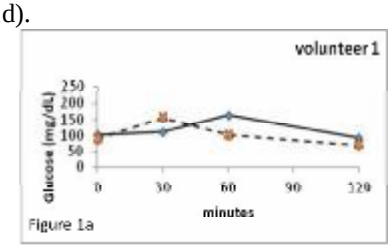
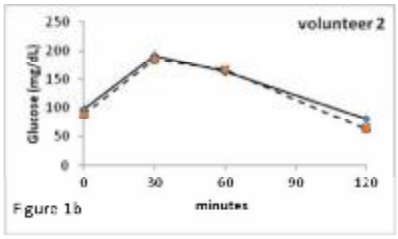
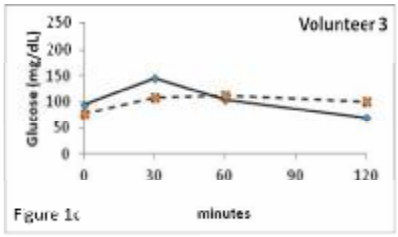
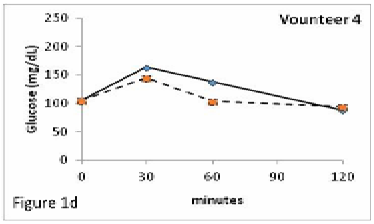


Figure 1a







Figures 1a, 1b, 1c, 1d: Patterns of OGTT response (—■—) basal OGTT, (.-■-.) OGTT after *AF* administration.

6- Results of diabetic patients: Diabetic patients (3male/2 female) presented the following anthropometric parameters (table 4).

Diabetes onset, medication, fasting blood glucose (FBG) results before using *A.F* are summarized in (table 5).

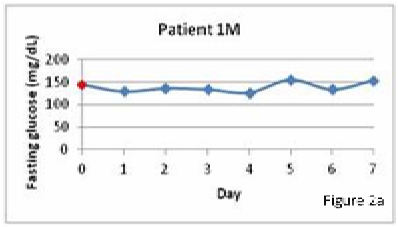
Table (4): anthropometric parameters of diabetic patients

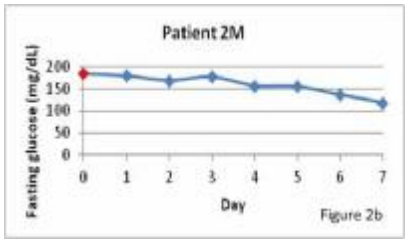
Patient	sex	Age	BMI	WHR
1	F	58	33.9	0.82
2	F	59	26.5	0.8
3	M	71	32.4	0.98
4	M	56	28.5	0.94
5	M	61	26.17	1

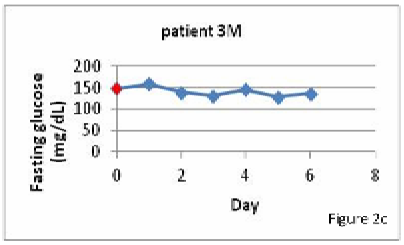
Table 5: Diabetic patients medication &history

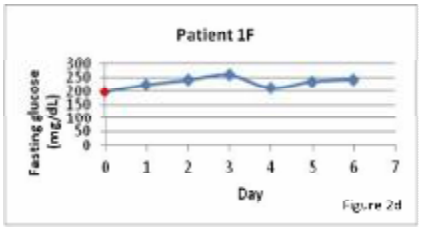
patient	Diabetes onset	Medications
1 F	5 years	Metformin - Gliclazide
2 F	14 years	Gliclazide –Metformine - sitagliptin- Insulin
1 M	6 years	No treatment
2 M	7 years	Metformin - Insulin
3 M	2 years	Metformin - Gliclazide

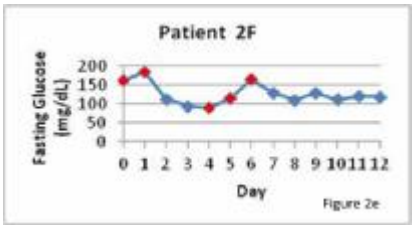
Fasting Blood Glucose results during one week of *A.F* extract consumption are shown in figures (2a, 2b, 2c, 2d, 2e). Two patients (patient 2M &2F) have shown decreasing in fasting blood glucose levels during the first week of *A.F* extract administration.











Figures 2a,2b,2c,2d,2e : Effect of *A.F* on Fasting Blood glucose in five Diabetic 3 male (M) & 2 female(F) patients during at least 7 days. Day (0) is the day before using *A.F* Patient 2F had stopped using AF for 3 days (in red) then continued.

Discussion

Medicinal plants have been used for centuries throughout the world, and many people still rely on

indigenous medicinal plants for their safe or primary health care needs[15]. There is an appreciable prevalence of herbal use among patients with diabetes in the Middle East region [4,15].

In Syria, based on the information from the herbalists and inhabitants, use of medicinal plants in Diabetes Mellitus management is well known. *Achillea* species are reputed as hypoglycemic specially *A.santolina*[4] and A. *fragrantissima*[16]. This effect could be attributed to the presence of flavonoids. Flavonoids are well-documented for an anti-diabetic activity[17] and *Achillea* genus is rich in flavonoid.

In our study, we detected the presence of flavonoids in the aqueous extract of *A. falcata*. In order to evaluate the effect of *A.F* extract on glucose absorption, we carried out oral glucose tolerance test (OGTT) in healthy volunteers. Our results revealed several patterns of response to *A.F* extract, among them: no change in OGTT curve shape or IAUC (incremental area under the curve) as in the case of volunteer 2, A diminution of IAUC as in cases of volunteer1 & volunteer 4 , or an increase in IAUC (volunteer 3). These patterns emphasis the importance of prolonged administration of a compound to study its effect.

From a statistical view the presence of important decrease in IAUC after *A.F* extract dose (p=0.05) would suggest an effect on glucose absorption. The suggested effect on glucose absorption was obvious in participants with strong family history in diabetes (1st dg) (p=0.03), although they all have a normal OGTT (FBG <100 mg/dl and 2-h plasma glucose <140 mg/dL) , but basal IAUC is more important significantly than IAUC in participants without any familial history of diabetes (p=0.004).

Diabetic patients who participated in this study used the extract in addition to their usual medication. Two of them (patient 2F & 2M) only responded to prolonged administration of the extract and fasting blood glucose had diminished.

Many reasons are responsible for this result, specifically the fact that Diabetes is a multifactorial disease with a lot of underlying mechanisms and the small size of studied sample .

Conclusion

Our study demonstrates that the aqueous extract of *Achillea Falcata* could have an hypoglycemic effect, which may support herbalist's traditional recipes, although further investigations are needed .The use of OGTT and the calculation of the incremental area under the curve are useful means for the estimation of body response to glucose overload in different circumstances.

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