Evaluation of the Antihyperglycemic Effect of N-butanol Leaves Extracts of Iraqi *Fumaria parviflora* in Alloxan-prompt Diabetic Rats

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Authors’ contributions

This work was carried out in collaboration between both authors. Author EJK designed the study, performed the statistical analysis and wrote the protocol. Author OHA wrote the first draft of the manuscript, managed the analyses of the study and complete wrote of manuscript (introduction, discussion, and reference) and managed the literature searches.

Article Information

DOI: 10.9734/JPRI/2019/v30i630287

Editor(s):
(1) Prof. Dr. Mostafa A. Shalaby, Professor of Pharmacology, Faculty of Vet. Medicine, Cairo University, Egypt.

Reviewer(s):
(1) Senthil Kumar Raju, Swamy Vivekanandha College of Pharmacy, India.
(2) Veeravan Lekskulchai, Srinakharinwirot University, Thailand.
(3) Miikue-Yobe, Nigeria.
(4) Maha Zaki Rizk, National Research Centre, Egypt.

Complete Peer review History: https://sdiarticle4.com/review-history/52019

Received 03 August 2019
Accepted 24 October 2019
Published 30 October 2019

ABSTRACT

**Objective:** In this research, we evaluated the antihyperglycemic effect of leaves of *Fumaria parviflora* (*F. parviflora*) and implied mechanisms by using in vivo models of hyperglycemia.

**Materials and Methods:** Fifty male Wistar rats weighing 180-220 g were applied for the research. Soxhlet ethanolic extract of leaves of *F. parviflora* (*EFP*) was prepared. Alloxan-induced diabetic rats were orally remedied with the extract (50, 100 or 200 mg/kg/day), metformin (200 mg/kg/day) for two weeks. Another animal received only extract, alloxan (diabetic control) or vehicle (control).

**Results:** pretreatment effect of plant extract on blood glucose levels of diabetic rats Blood glucose levels in all extract pretreated groups was lower (p<0.05) when compared with the levels in rats that

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INTRODUCTION

The uses of a medicinal plant for cure specific ailments have been invoked from ancient times. Nature has bestowed mankind with several plants that contain natural substances that cure diseases & enhance health. Such medicinal plants were also rich sources to develop secondary metabolites which also scope for curing different ailments. In the last decades, this is increased attention and benefit in the use of herbal medicines globally [1].

Diabetes Mellitus metabolic disorder characterized by inappropriate hyperglycemia caused by an as relative or absolute deficiency of insulin or by opposition to the action of insulin at the cellular level is found for all parts of the world [2]. The longer expression complications thought be cardiovascular disease, nerve damage, chronic kidney failure, retinal damage, and scanty healing at wounds, followed by gangrene on the feet leading to resection [3].

It has been well known that these complications bring on significant morbidity and mortality statistics worldwide, which is affecting negatively of quality of life in patients with diabetes. Diabetes mellitus, is a multifactorial disease, desire multiple therapeutic approaches. Global studies in diabetes mellitus have refined that primary prevention is necessary and drastic steps should be taken to diagnose the disease early, provide effective management and also take steps for preventing the onset of disease in high-risk subjects [4]. *Fumaria parviflora* Lam. (Fumariaceae) is an annual herbaceous plant that implants in various parts of are Indo-Pakistan subcontinent, Middle East and South Asia. It is commonly known as a fine leaf fumitory, Indian fumitory or wax dolls of English [5]. It has been conventionally used in Greco-Arab (Unani) traditional medicine and Iranian folk medicine for liver, bile duct, and gut disorders, dermatological diseases such as acne, eczema, and scabies and diuretic, antipyretic, expectorant, diaphoretic and antineoplastic agent [6].

It is known of Shahtareh in Iran and aerial parts of *F. parviflora* have been used traditionally in Iranian folk medicine against liver and bile duct disorders, diuretic and laxative and for it's male fertility-promoting properties [7-10]. It is also considered the treatment of hepatobiliary disorders and as a blood purifier [11-15]. Phytochemical analyses of some plants in the genus Fumaria, including *F. parviflora*, has indicated the existence in isoquinoline alkaloids namely protopine, cryptopine, style pine, bicusuline, parfumine, fumariline, fumaritine, dihydrofumariline, perfumidine and dihydrosanguinarine [16]. It had been reported that *F. parviflora* and *F. vaillantii* other species of genus Fumaria have power for counteracting CCl4 induced hepatotoxicity due to their antioxidative properties [17, 18].

The Oral administration of Lam. *Fumaria Parviflora* powder for streptozocin-induced diabetic rats afffict triglyceride, total cholesterol, and HDL serum levels, but no significant effect of serum glucose and LDL [19, 20]. In other studies the hypoglycaemic effects of methanolic extract in normal and *Fumaria parviflora* alloxan-induced diabetic rats. Administration of *Fumaria parviflora* extract showed potent glucose-lowering effect only at streptozotocin-induced diabetic rats below 100 mg/dl [21].

KEYWORDS: *Fumaria parviflora*; alloxan-induced diabetes rats; hyperglycemia effects.

Conclusion: Leaves of *F. parviflora* possess blood glucose-lowering effects. In Alloxan-Induced Diabetic Rat, The findings of a study indicated that *F. parviflora* has a significant hypoglycemic effect on Alloxan-induced diabetic rats with no effects in blood glucose levels of normal rats.

2. MATERIALS AND METHODS

2.1 Plant Extraction

The Iraqi *Fumaria parviflora* plant was collected from Erbil North of Iraq, at September 2017. The plant was identified and authenticated by the Department of Biology, College of the Sciences University of Baghdad.
2.2 Preparation of Plant Extract

The dried leaves of *F. parviflora* (1.5 kg) were coarsely powdered and extracted with 85% methanol for 48 h using a Soxhlet extractor in a hot and cold cycle of an interval of 5-6 hrs. The extract was dried under reduced pressure for obtaining a dark brown residue. The extract was partitioned with hexane (100 ml X 3) and chloroform (100 ml X 3) and excluded. The remaining portion of extract (70 g) was portioned with normal butanol (100 ml X 3). Normal butanol fraction was taken and dried under reduced pressure, weighed and preserved in refrigerated at 4°C for the experiments.

2.3 Animals and Experimental Design

Alloxan-induced diabetic rats were orally pre and post-treated with extract (50, 100 or 200 mg/kg/day), metformin (200 mg/kg/day) for two weeks. Another group received only extract, alloxan (diabetic control) or vehicle (control). Fifty male Wistar rats weighing 180-220 g were used for this study. That was obtained from the animal house of the Al-Naharin University medical department. These rats were maintained under natural room temperature (27±5°C) and lighting conditions, housed in cages in a ventilated room, fed with standard rodent diet and given tap water.

The animals were randomized into ten groups (1-10) containing 5 rats each.

Group 1: Those animals were given 0.5 ml DMSO plus distilled water (2:3) daily for 2 weeks. Blood was sampled for beginning (day 1) and twice-weekly (on days 3, 7, 11 and 14) to measure glucose levels in these animals.

Group 2: Animals were injected intraperitoneally with as a single dose of alloxan (120 mg/kg) to induce diabetes [22]. The rats were fasted overnight for 12-14 h but allowed access to water before alloxan administration. Blood glucose level was measured for the beginning and twice weekly for 2 weeks.

Groups 3 and 4: Their animals were pretreated with plant extract (50, 100 or 200 mg/kg, PO) daily for 14 days, followed by induction of diabetes with alloxan and observed for 2 weeks. Blood glucose level was measured at the beginning and twice-weekly after the alloxan administration.

Groups 5, 6, 7 and 8: Animals were injected alloxan, followed by treatment with a plant extract (50, 100 or 200 mg/kg, PO), metformin (200 mg/kg, PO) daily for 2 weeks. Blood glucose level was measured for beginning and twice-weekly after extract and drug administration.

Groups 9 and 10: Animals were administered plant extract (50, 100 or 200 mg/kg, PO) daily for 14 days. Blood glucose level was measured for beginning and twice weekly.

The doses of metformin used are equivalent to the therapeutic dose levels [23].

Alloxan was dissolved in distilled water, while extract was dissolved in 40% DMSO. Extract and drug solutions that administered with a 1 ml syringe and oropharyngeal cannula. Blood glucose level was measured with an Accu-Check® active glucometer. Animals fasted overnight for 12-14 h on days for sampling, and blood samples were obtained using the tail nipping method [24-26].

3. RESULTS

3.1 Study on Protective Effect

Effect of plant extracts pretreatment of blood glucose levels in diabetic rats. Blood glucose levels in all extract pretreated groups their lower (p<0.05) when contrast with the levels in rats there received alloxan alone (Table 1). However, the glucose levels in pretreated groups were higher (p<0.01) compared for control except for 200 mg/kg pretreated group where blood glucose levels became comparable with this observation on days 11 and 14 (Table 1). The intra-group comparison showed that glucose levels in 50 or 100 mg/kg extract administered groups that higher than the 200 mg/kg extract-treated group Table 1 is phytochemical screening.

3.2 Study on Ameliorative Effect

Blood glucose levels in the rats were administered and extract were lowered (p<0.05) dose-dependently through the 14 days treatment period, compared as alloxan alone treated rats. However, glucose levels in extract-treated rats on sampling days 3, 7 and 11 were reported higher than the control treatment. At day 14, glucose level in the control (71.00±2.88 mg/dl) was similar (p>0.05) with that in-group that received 100 mg/kg extract (81.00±1.5 mg/dl), however lower (p<0.05) in the group that
received 200 mg/kg extract, 45.00±3.53 mg/dl (Table 2). In addition, glucose levels in metformin administered rats that reduced (p<0.05) over the treatment duration compared to alloxan alone treated rats. As well, whereas glucose level in metformin-treated rats was not significantly different from control on day 14, all other metformin-induced glucose levels were higher than control (Table 2). Where compared with metformin, glucose levels of extract-treated animals were not different on days 3 or 11, but prolonged on day 7 (Table 2). On the 14th day, glucose level in rats where  received the smallest dose of extract (50 mg/kg) was higher, while the glucose level in rats that received the highest dose (200 mg/kg) was lower when compared to metformin.

3.3 Effect of Plant Extract on Blood Glucose Levels in Normal Wistar Rats

Rats that were treated with plant extract had normal blood glucose levels which spread from 73.00±1.5 to 76.00±0.54 mg/dl at the beginning (first day) of the experiment. Blood glucose levels in those animals declined during the period of the plant extract administration, but the values obtained were not significant compared to control exclude those that were obtained on the 14th day, p < 0.05.

Table 1. Phytochemical test of a plant extract

<table>
<thead>
<tr>
<th>Phytochemicals</th>
<th>Flavonoids</th>
<th>Saponins</th>
<th>Sterols</th>
<th>Phenols</th>
<th>Alkaloids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plant extract</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Table 2. Blood glucose levels after injection of alloxan (allox) in n-butanol fumaria extract (bfe) pretreated the wistar rats (mg/dl)

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 11</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>75± 1.5</td>
<td>72± 2.5</td>
<td>70± 2.11</td>
<td>73± 1.9</td>
<td>73± 2.88</td>
</tr>
<tr>
<td>Allox</td>
<td>74± 0.44</td>
<td>400±5.66***</td>
<td>420±4.22***</td>
<td>405±1.5***</td>
<td>390±5.58**</td>
</tr>
<tr>
<td>BFE(50mg/kg)+allox</td>
<td>73± 2.5</td>
<td>305±2.33**</td>
<td>250±0.33***</td>
<td>210±1.5**</td>
<td>190±4.22**</td>
</tr>
<tr>
<td>BFE(100mg/kg)+allox</td>
<td>74± 2.5</td>
<td>290±5.5***</td>
<td>244±6.11**</td>
<td>195±1.5**</td>
<td>140±1.5**</td>
</tr>
<tr>
<td>BFE(200mg/kg)+allox</td>
<td>74± 2.44</td>
<td>288±1.98**</td>
<td>195±2.5*</td>
<td>110±3.45*</td>
<td>70±3.5*</td>
</tr>
</tbody>
</table>
| Data includes as mean±SEM, n=5 rats per group; * ASignificant compared to control at p<0.05; ** Significant compared to control at p<0.01; *** Significant compared to control at p<0.0001; # A Significant compared to alloxan at p<0.05; aA Significant compared to extract (200 mg/kg) at p<0.05

Table 3. Effects of n-butanol fumaria extract (BFE), metformin (MET) on alloxan (ALLOX)-induced hyperglycemia in a wistar rats (study on ameliorative effect) (MG/DL)

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 11</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>74± 0.32</td>
<td>73± 0.5</td>
<td>71± 1.11</td>
<td>70± 1.01</td>
<td>71± 2.88</td>
</tr>
<tr>
<td>Allox</td>
<td>71± 0.44</td>
<td>420±5.16***</td>
<td>410±3.22***</td>
<td>400±1.5***</td>
<td>380±5.58***</td>
</tr>
<tr>
<td>Allox+BFE(50mg/kg)</td>
<td>70± 2.5</td>
<td>430±6.33**</td>
<td>320±5.33***</td>
<td>200±11.5**</td>
<td>140±2.22**</td>
</tr>
<tr>
<td>Allox+BFE(100mg/kg)</td>
<td>72± 1.5</td>
<td>420±1.5***</td>
<td>300±6.11***</td>
<td>165±11.5#</td>
<td>81±1.5#</td>
</tr>
<tr>
<td>Allox+BFE(200mg/kg)</td>
<td>70± 2.44</td>
<td>400±1.98***</td>
<td>280±2.5**</td>
<td>115±2.45#</td>
<td>45±3.53#</td>
</tr>
<tr>
<td>Allox+Met</td>
<td>70± 2.44</td>
<td>433±1.98***</td>
<td>260±2.5**</td>
<td>180±3.45*</td>
<td>110±3.5*</td>
</tr>
</tbody>
</table>
| Data includes mean±SEM, n=5 rats per group; * A Significant compared to control at p<0.05; ** Significant compared to control at p<0.01; *** Significant compared to control at p<0.0001; # A Significant compared to alloxan at p<0.05; a Significant compared to extract (200 mg/kg) at p<0.05

Table 4. Blood glucose levels in a normal wistar rats following 14 days daily treatment with normal butanol fraction of Fumaria parviflora extract, blood glucose concentration (MG/DL)

<table>
<thead>
<tr>
<th>Dose Mg/Kg</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 11</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>75± 0.22</td>
<td>71± 0.5</td>
<td>73± 2.11</td>
<td>73± 1.01</td>
<td>72± 1.7</td>
</tr>
<tr>
<td>50</td>
<td>76± 0.54</td>
<td>70± 1.7</td>
<td>69± 2.2</td>
<td>55± 1.5</td>
<td>44± 5.5*</td>
</tr>
<tr>
<td>100</td>
<td>73± 1.5</td>
<td>70± 1.3</td>
<td>70± 1.2</td>
<td>53± 3.4</td>
<td>41± 2.2*</td>
</tr>
<tr>
<td>200</td>
<td>70± 1.5</td>
<td>70± 0.5</td>
<td>62± 1.1</td>
<td>50± 0.5</td>
<td>40± 1.5*</td>
</tr>
</tbody>
</table>
| Data expressed as mean±SEM, n=5 rats per group; * A Significant compared to control at p<0.05
4. DISCUSSION

The use of medicinal plants in the remediation of diseases has been a substantial part of medicinal therapy as observed for thousands of years participating in a scientific search of safer phytotherapeutic products, this regard [20]. Ever-increasing diabetes mellitus draws scores of researchers' attention in that phenomenon as a serious threat to mankind's health in all parts of the world. In spite of the traditional use of botanicals in the treatment of diabetes, the rarity of definitive data on the efficacy of those herbal remedies still deals with a challenge in this field. The results mark that the extracts of *Fumaria parviflora* lowered the blood glucose level in the normal animals. The hypoglycemic effect observed in the normal rats offers these extracts possess as a pharmacological effect. Those plants may contain several hypoglycemic principles that probably act by initiating the release of the insulin from the pancreatic b-cells of normal animals (sulfonylurea-like effect) [27].

Alloxan administration at the dosage of (120 mg/kg) to prompt diabetes to normal rats safely elevated the blood glucose levels. Their results indicate that the extracts of *Fumaria parviflora* lower the blood glucose levels of Alloxan diabetic rats. Administration of Alloxan selectively destroys the b-cells of the islets of Langerhans [28]. The destruction of b-cells This causes the marked lower in a insulin levels. The hypoglycemic action of the extract in diabetic rats might be possible through the insulin-mimetic action or by other mechanisms such as stimulation of glucose uptake by peripheral tissues, suppression of endogenous glucose production, or activation of gluconeogenesis in liver and muscles. A similar mechanisms have been reported for plant extracts with antidiabetic activity [29]. Moreover, investigations were required to determine the exact cellular and molecular mechanisms of the antidiabetic activity of *Fumaria parviflora* extracts. In the conclusion part, our study indicates that the aqueous extracts exhibited activity both in a normal and Alloxan -prompt diabetic rats.

*Fumaria parviflora* extract was prepared by partitioned alcoholic extract with n-butanol after they excluded hexane & chloroform extract, n-butanol part contains phenolic and flavonoids constituents that play a very important function in the management of diabetic. Flavonoids had been identified to be good inhibitors of aldose reductase [30]. It had been reported by several researchers that several flavonols possess anti-diabetic activity, ago it brings about regeneration of pancreatic islets and increases insulin release in streptozotocin-induced diabetes, and also, it had been reported to activate Ca2+ uptake from isolated islet cells thus suggesting it to the effect even in type-2 D.M [31].

5. CONCLUSION

The current investigation is evidence of the antidiabetic activity of *F. parviflora* in Alloxan-induced diabetic rats. The authors believe that *F. parviflora* could be considered as an excellent candidate of further study on verifying the mechanisms of hypoglycemic activity, as well as for segregation and identification of the foremost hypoglycemic phytochemical responsible for the anti-diabetic activity of a plant. Besides, further comprehensive pharmacological surveys, including experimental chronic studies, could be of value to assess the possible toxicological effects of this anti-diabetic plant.

CONSENT

It is not applicable.
ETHICAL APPROVAL

As per international standard written ethical permission has been collected and preserved by the author(s).

ACKNOWLEDGEMENTS

Financial support of this study by the Research college of pharmacy University of Baghdad is faith fully appreciated.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


