

Hypoglycemic Activity of *Fagonia indica* and *Aloe vera* in Alloxan-Induced Hyperglycemia in Mice

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Abstract

Aloe vera and *Fagonia indica* are two plants growing in UAE and widely used in the folk medicine as to produce a lowering effect on blood glucose level in diabetics. The aim of the present study was to investigate the effect of these plants extracts alone and in combination on blood glucose level of alloxan-induced hyperglycemia in mice. Mice were injected intraperitoneally with alloxan monohydrate at a dose of 150 mg/kg to elevate the blood glucose level. After 72 hours, fasting blood glucose level was measured following a fasting period of 16 hours. Mice with values more than 250 mg/dl were considered hyperglycemic and selected to continue the experiment. Following treatment with either *Aloe vera* (500 mg/kg) or *Fagonia indica* (500 mg/kg) or their combination, blood samples were collected at intervals of 0, 1, 2, 3 and 5 hours, and blood glucose level estimated. Both plants, either alone or in combination, succeeded in lowering blood glucose level in mice on an acute basis. Moreover, 15 days treatment with combination of both herbs significantly reduced blood glucose level. It can be concluded that *Fagonia indica* alone or combined to *Aloe vera* can be used as a natural blood glucose lowering agent and that the traditional use of these agents in combination is justified.

Keywords: *Fagonia indica*; *Aloe vera*; Hyperglycemia; Diabetes; Alloxan; Blood glucose level

Abbreviations: BGL: Blood glucose level; CMC: Carboxy methyl cellulose; SD: Standard deviation; ANOVA: Analysis of variance; HMW: High molecular weight; LMW: Low molecular weight

Introduction

The important values of some plants have long been published but a large number of them remain unexplored as yet. So there is a necessity to explore their uses and to conduct pharmacognostic and pharmacological studies to ascertain their therapeutic properties. Approximately 343 plants of the world have been screened for the ability to lower blood glucose in the laboratory experiments. Of them, 158 species are claimed to be used in the Ayurveda medicine [1].

Fagonia is a genus of flowering plants in the Zygophyllaceae family found in deserts and dry areas from India to Tropical Africa and in Chile as well as USA. In UAE, it is widespread, found in shallow sands over gravels or limestone and hillsides. In folk medicine, *Fagonia indica* is used as a hypoglycemic agent and was reported by some literature to be effective in mixture with *Aloe vera* and *Tylophora hirsuta* L. in lowering the BGL among the rural inhabitants of the area of study [2].

Aloe Vera has been medicinally used throughout history by many different cultures but only recently studied as a treatment for diabetes. In the folk medicine, *Aloe vera* serves as an important alternative source in the management of hyperglycemia helping reducing increased BGL [3]. A number of promising experimental as well as clinical studies have demonstrated the anti-diabetic effects of the inner gel of the *Aloe vera* leaf [4,5].

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The aim of the present study was to screen the alcoholic extract of *Fagonia indica* whole plant for its possible effect regarding lowering of BGL of alloxan-induced hyperglycemic mice. Combination of *Fagonia indica* extract with *Aloe vera* gel was also tested for its hypoglycemic activity as the mixture is already used in the folk medicine.

Materials and Methods

Materials

Chemicals: Ethanol 95% obtained from E. Merck (Germany). Alloxan monohydrate obtained from Sigma-Aldrich (USA).

Animals: Healthy male Swiss albino mice, weighing 20-25g, were obtained from the animal house facility of Lootah Technical Centre. Mice were housed in an environmentally controlled room (with 12 hours light/dark cycle) before and during the experiment. They were allowed to receive standard chow diet and tap water throughout the experimental period except for the fasting period during which the animals were individually caged. Mice were carefully marked for identification of each particular animal. The study was carried out according to the ethics of animal handling and approved (Reference: #PT013.04.16) by the Ethical Committee for Animal Experimentation at Dubai Pharmacy College.

Methods

Preparation of plants extracts

***Fagonia indica* alcoholic extract:** The whole plant of *Fagonia indica* Burm f. was collected during September till October (2013) from the desert plants growing in Muhaisna desert, Dubai, United Arab Emirates. Plant's identity was kindly verified by Prof. Hassnaa Ahmed Hosny, Professor of Plant Taxonomy, Department of Botany, Faculty of Science, Cairo University, Egypt. Voucher specimens were kept at the Herbarium of the Pharmacognosy Department, Faculty of Pharmacy, Cairo University and at the herbarium of Dubai Pharmacy College (Reference: #013.10.22). The alcoholic extract was obtained by exhaustive cold maceration of the air-dried powdered plant material (200g) in 70% ethanol (1L×2). The collective alcoholic extracts were then evaporated to dryness under vacuum at a temperature not exceeding 50°C. The solvent-free residue (15g) was dissolved in CMC 1% and kept for biological study.

Aloe vera extract

The leaves were collected during January 2014. The juice was freshly prepared by cutting the leaves (1 kg) by knife, then the gel was separated and grinded with 70% alcohol (2L) using a blender.

Phytochemical screening

Samples of air-dried powdered plant of *Fagonia indica* and fresh gel of *Aloe vera* were subjected to tests for different constituents' viz. carbohydrates, flavonoids, tannins, unsaturated sterols and/or triterpenes, alkaloids, saponins, anthraquinones and cardiac glycosides [6].

Animal Studies

Acute toxicity study

The acute toxicity of *Fagonia indica* alcoholic extract was previously tested and method as well as results published by the authors [7]. In brief, oral administration of several doses of the extract ranging from 30mg to 4g per kg to different groups of mice was carried out. Mortality was assessed over two consecutive days and animals were observed for any illness or abnormal behavior. For *Aloe vera*, its safety was guaranteed by a previously-published study which estimated its LD₅₀ to be 4.8 g/kg [8].

Alloxan-induced diabetes mellitus model

Animals were i.p injected with a single dose of alloxan monohydrate (150 mg/kg) [9]. Three days after alloxan administration, fasting BGL was estimated using a blood glucometer following a fasting period of 16 hours. Values more than 250 mg/dl were considered hyperglycemic. On the other hand, animals which will serve as non-diabetic control group were injected saline in the same manner the diabetic animals were treated.

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Acute hypoglycemic study

Hyperglycemic mice were thereafter divided into four groups and treated according to the following schedule:

1. Group I: Diabetic control (received the vehicle CMC).
2. Group II: *Aloe vera*-treated (500 mg/kg).
3. Group III: *Fagonia indica*-treated (500 mg/kg).
4. Group IV: Combination-treated (*Aloe vera* + *Fagonia indica* at a dose of 500 mg/kg for each)

Another group of animals received distilled water and served as normal control group. All the extracts, distilled water and the vehicle were given orally to animals fasting overnight.

Sub-acute hypoglycemic study

Another set of animals were made hyperglycemic by the same method of induction then only hyperglycemic animals were used for the study. *Aloe vera* plus *Fagonia indica* at a dose of 500 mg/kg/day for each plant was orally administered to mice on a daily basis for 15 days. A group of hyperglycemic animals (receiving the vehicle CMC) and another group of normal animals (receiving distilled water) were also used as control diabetic and normal groups respectively.

Estimation of BGL

Blood samples were collected from the tip of the tail and BGL measured by the glucometer 1, 2, 3 and 5 hours after treatment administration (for acute experiment) and once in the morning (for the sub-acute experiment). Average of readings at each time point was obtained and plotted in a comparative graph.

Statistical Analysis

Results were expressed as mean \pm SD. Differences among means were tested for statistical significance by one way ANOVA. When differences were significant, Tukey-Kramer's test was used for multiple comparisons between groups. Statistical significance was considered at $p < 0.05$.

Results

The results of the present investigation revealed a hypoglycemic effect of the ethanolic extract of *Fagonia indica* as well as the gel of *Aloe vera* on an acute basis (Figure 1). We tried in this study to combine both *Fagonia indica* extract and *Aloe vera* gel in order to test the potential of the combination in lowering BGL since it is usually used as a mixture in the folk medicine [2]. Both plants, alone and in combination, produced a significant fall in BGL in the alloxan-induced hyperglycemic mice. Measurement was done at 1, 2, 3 and 5 hrs following treatment with either of the extracts where the BGL lowering effect significantly appeared starting the first hour and reached highest value at the fifth hour. BGL values after 5 hours were 241.5 ± 12.58 , 303.86 ± 11.71 and 267.42 ± 17.76 vs 521.57 ± 17.84 mg/dl for the *Aloe vera*-treated, *Fagonia indica*-treated and combination-treated versus diabetic control untreated group respectively (Figure 1).

Moreover, treatment with both herbs was tested on a longer time basis and results demonstrated that it is effective in gradually reducing the BGL of hyperglycemic mice during a 15 days period. Measurement was done 5, 10 and 15 days following daily oral treatment with a combination of both *Aloe vera* gel and *Fagonia indica* extract. Lowering of BGL was gradually increasing with time reaching 35.56% reduction after 15 days (Figure 2).

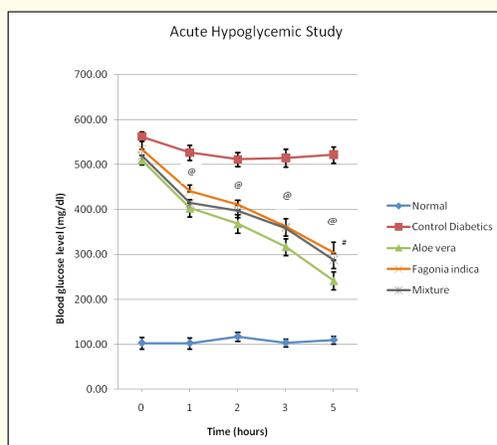


Figure 1: Acute effect of *Fagonia indica* and *Aloe vera* alone and in combination on hyperglycemia induced by alloxan in mice. A dose of 150 mg/kg of alloxan was i.p. injected to induce hyperglycemia and after 72 hours, mice with values of fasting BGL higher than 250 mg/dl were considered hyperglycemic and used for the study. Both *Fagonia indica* and *Aloe vera* were administered by oral gavage at a dose of 500 mg/kg for each either alone or in combination. Results are means \pm SD of 7-10 animals. Statistical analysis was performed by one way ANOVA followed by Tukey Kramer's multiple comparison tests. Results are considered significant at $p < 0.05$. All values of the four treatment groups are significantly different from normal group values at the corresponding time. @: significantly different from control hyperglycemic group. #: significantly different from *Aloe vera*-treated group.

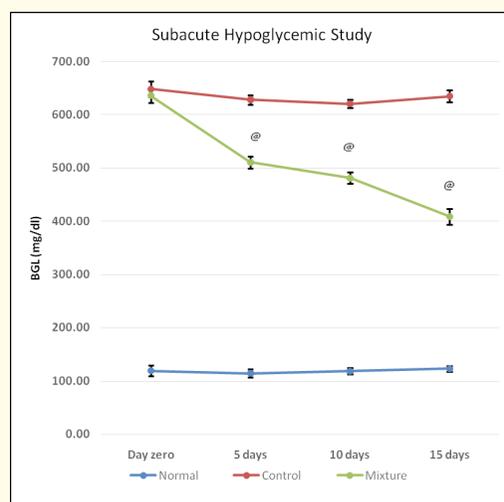


Figure 2: Effect of two weeks treatment with *Fagonia indica* and *Aloe vera* in combination on hyperglycemia induced by alloxan in mice. A dose of 150 mg/kg of alloxan was i.p. injected to induce hyperglycemia and after 72 hours, mice with values of fasting BGL higher than 250 mg/dl were considered hyperglycemic and used for the study. Both *Fagonia indica* and *Aloe vera* were administered by oral gavage at a dose of 500 mg/kg for each in combination for 15 days. Results are means \pm SD of 8-12 animals. Statistical analysis was performed by one way ANOVA followed by Tukey Kramer's multiple comparison test. Results are considered significant at $p < 0.05$. All values are significantly different from normal group values at the corresponding time. @: significantly different from control hyperglycemic group.

Discussion

The hypoglycemic effect of *Fagonia indica* may be attributed to the high phenolic contents especially quercetin aglycone (3%) and its glycoside that have been earlier isolated from the plant by the authors [7]. According to the mentioned study, these isolated constituents exhibited strong antioxidant effects. This is in accordance with a previous study which showed that quercetin significantly decreased the BGL of streptozotocin-induced diabetic rats [10]. It was also reported that quercetin, a flavonoid with antioxidant properties, usually brings about the regeneration of the pancreatic islets and probably increases insulin release in streptozotocin-induced diabetic rats; thus exerting its beneficial antidiabetic effects [11]. The chemical constituents of *Fagonia indica* were also demonstrated to be consisting of triterpenoids, saponins, alkaloids, coumarins, flavonoids and tannins [12]. These constituents may be responsible, at least in part, for its ability to lower BGL. In accordance with this assumption, phytochemical testing of *Fagonia indica* achieved in the present study revealed the presence of carbohydrates, flavonoids, tannins and triterpenes (Table 1).

Constituents	<i>Fagonia indica</i>	<i>Aloe vera</i> gel
Carbohydrates	+ve	+ve
Flavonoids	+ve	-ve
Anthraquinones	-ve	traces
Cardiac glycosides	-ve	-ve
Tannins	+ve	-ve
Saponins	-ve	-ve
Alkaloids	-ve	-ve
Unsaturated sterols and/or triterpenes	+ve	-ve

Table 1: Active constituents of *Fagonia indica* and *Aloe vera* gel as detected by phytochemical screening.

The exudates of the *Aloe vera* plant contain many compounds those have been therapeutically used by humans [2]. According to a previous study, *Aloe Vera* may be among the most beneficial substances for diabetics looking to regulate blood sugar levels naturally [13]. *Aloe vera* gel was historically claimed to possess antidiabetic activity. Clinical trials for the *Aloe vera* gel were investigated and results revealed that oral administration of *Aloe vera* juice twice a day for at least 2 weeks in patients with diabetes significantly reduced the blood sugar and triglyceride levels in the treated patient group [4]. Carbohydrates were found to be the main constituent of *Aloe vera* gel tested in the present study (Table 1). The possible hypoglycemic effect of *Aloe vera* may be due to HMW polysaccharides present in the gel [14]. Indeed, compared in a previous study, the HMW polysaccharides were proven to produce more significant lowering of blood sugar in rats than the LMW polysaccharides [15].

Conclusion

In combination, these two herbal products are justified for their abilities to lower the BGL of hyperglycemic mice in the present work and it is concluded that they can be recommended for individuals aiming at managing their diabetes naturally. Further detailed researches are required to elaborate the specific constituent(s) responsible for the activity of *Fagonia indica* extract as hypoglycemic agent since this finding is novel to the phytochemical research. A Different dose range of the extract might be tried as well as comparing the potency of the extract against a standard BGL lowering medication should be targeted.

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