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A preliminary evaluation of effects of high doses of *Jujube* and *Saffron* on biochemical and hematological parameters in rats

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Abstract

We investigated effects of high doses of Jujube fruits and Saffron petals on biochemical and hematological biomarkers in rats. During 14 days treatment of herbs, mortality was not observed. No difference reported in FBS, lipid profile, total protein, albumin, total bilirubin and hematological parameters of rats after treatments. BUN, cratinine, urate and liver enzymes levels in both extracts increased. These changes were more noticeable in Saffron compared with Jujube. This study can suggest that administration of high doses of Jujube (up 5000 mg/kg) and Saffron (up 2000 mg/kg) are nearly safe, also did not exert hepato and nephrotoxicity in rats.

Keywords: Saffron, Jujube, Liver enzymes, Hematological parameters, In vivo

Findings

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Background

Medicinal plants have commonly been used for different diseases, such as Alzheimer [1], atherosclerosis [2], diabetes mellitus [3], cancer [4] and gastrointestinal diseases [5]. Although these plants are considered to be organic and safe, however may cause damage due to their unwanted side effects [6]. Therefore, studying effects of high doses of medicinal plants would have effective role in identifying of their safety profile in humans [7].

Ziziphus jujube M. (Jujube, J) and Crocus sativus L, (Saffron, S) belonging to the Rhamnaceous and Iridaceae families respectively [8]. These herbs grows mostly in southern and eastern Asia, especially Iran [9]. Saffron petal is a by-product of saffron and is usually discarded as a waste [10]. Recently it has been reported multiple biological effects of both herbs including antioxidant, anti-inflammatory, anti-cancer and regulating of blood sugar and lipid [11]. Like other plants, Saffron petals and Jujube fruits contained chemical components such as H_2O, carbohydrates, lipids, proteins and minerals and many bioactive compounds including triterpenic acids, flavonoids, cerebrosides, phenolic acids, α-tocopherol, β-carotene [12].

Firstly it is essential to investigate toxic doses of herbs in animal model to avoid potential harmful *effects* when used as medicine. This study evaluated properties of Saffron petals and Jujube fruits on their high doses-induced changes in blood biochemical markers in rats.

Methods

Preparation of plant extracts

Fresh-ripended fruits of Jujube and petals of Saffron were collected from Birjand, South Khorassan, Iran from September to October, 2014. These were dried in shadow then ground with a grinder (Hamilton Beach Brand, Canada). Aqueous extracts were prepared using 5 g of dried powder in 100 ml of boiling water for 2 h. The mixtures were filtered through a No. 1 Whatman filter paper and thus oven-dried at 40 °C for 24 h. Eventually, the samples lyophilized by freezing at – 80 °C for 24 h [13]. The crude extracts were dissolved in distilled water just prior to oral administration. Each extract was administered in five doses equal to 150, 500, 1000, 2000 and 5000 mg/kg body weight. The voucher number of specimen for Saffron (H. No. 2669) and for Jujube (H. No. 2470) was deposited in the Herbarium of Birjand University, Iran.

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Ferric Reducing Antioxidant Power (FRAP) assay

The total antioxidant capacity of herbal extracts was determined by FRAP assay [14]. The results were expressed in MFe (II)/g dry weight of plant extracts (DW).

Folin–Ciocalteu assay

The total phenolic contents of herbal extracts were measured using the Folin Ciocalteu method [15]. The data were expressed as milligram Gallic acid equivalents (GAE)/g dried weight of plant extracts (DW).

Determination of Total monomeric anthocyanins (TMA)

The TMA have been estimated by a pH differential method [16] using UV–Vis spectrophotometer. Results were expressed as mg of cyanidin-3-glucoside equivalents per liter of herbal extracts.

Animal experiments

Male Wistar rats (6–8-old-week; 200 ± 20 g) were purchased from animal house of Birjand University of Medical Sciences, Iran. All animal procedures were approved by the Animal Ethical Committee in accordance with the Guidelines for the Care and Use of Laboratory Animals prepared by this university. Rats were individually housed in a thermally controlled (25 ± 2 °C) room free from any sources of chemical contamination. Light was maintained on a 12 h dark–light cycle, and rats were fed a standard laboratory diet of rat chow (Javaneh Khorasan Co, Mashhad, Iran) with free access to tap water.

Study design

Animals were acclimatized to the laboratory conditions for the duration of ten days before the commencement of the experiment. 77 Rats were randomly assigned to 11 groups ($n = 7$/cage) and were weighed weekly. Experimental groups J1 and S1, J2 and S2, J3 and S3, J4 and S4 and J5 and S5 were received extracts at 150, 500, 1000, 2000 and 5000 mg/kg by gavage, respectively, for 14 days. Healthy control group (C) was gavaged with normal saline during this period. The used doses of herbs were based on Ahmad study [17].

Sample preparation

At the end of study blood was collected in sterile vial with and without anticoagulant for whole blood and serum separation respectively.

Hematology analysis

Red Blood Cells (RBC), Hemoglobin (Hb), Packed Cell Volume (PCV), Total White Blood Cells (WBC), Leukocyte Count (DLC) and thrombocyte count was estimated using an automated blood analyzer (Cell Dyn®3700, Abbott Dignostic, USA).

Biochemical analysis

Sera samples were analyzed for biochemical parameters such as Fasting Blood Suger (FBS), lipid profile (cholesterol, triglyceride, LDL, HDL), total protein, albumin, total bilirubin, using standard commercial kits (Pars Azmoon, Tehran, Iran).

Assessment of liver function

Serum Alanine Amino Teransferases (ALT/SGPT), Aspartate Amino Teransferases (AST/SGOT), Lactate Dehydrogenase (LDH), Alkaline Phosphatase (ALP), were determined to check the function of liver.

Assessment of kidney function

Blood Urea Nitrogen (BUN), cratinine and uric Acid using standard commercial kits (Pars Azmoon, Tehran, Iran) were evaluated to control the function of kidneys.

Statistical analysis

Results were expressed as the mean ± SD of the indicated number of independent experiments. The Student-T test was used to compare the mean values of different parameters obtained in various groups by employing SPSS (version 18) software and $P < 0.05$ were considered as significant.

Results

Total antioxidant activity (TAA)

The FRAP values of adequate concentrations of both extracts (2.5 g/l) indicated in Table 1. Total antioxidant activity expressed in M Fe(II) per gram dry weight (DW) of plant extracts.

Total phenolics contents (TPC)

The results of total phenolic values of herbs (2.5 g/l) are presented in Table 1. Total phenol content expressed in milligrams of Gallic acid equivalents (GAE) per gram dried weight (DW) of plant extracts.

Total anthocyanins contents (TAC)

Total monomeric anthocyanins of extracts are shown in Table 1. Total monomeric anthocyamins expressed as mg cy-3-glu per liter of plant extracts.

Effects of herbs on rat's survival and body weight

The results revealed that no significant differences in survival were observed between groups, with approximately 98 % of the animals surviving to study termination. Table 2 showed the changes in weight of all animals during the experiment as well as the lower weight of animals in the S5-treated group. The mean body weights of rats receiving J1-J5 and S1-S5 did not significantly ($P < 0.05$) differ from controls (Group C) over time.

Effects of herbs on hematological parameters

Our data illustrated that treated rats (Groups J1-J5 and S1-S5) did not exhibited significant difference in RBC, Hb and PCV, platelet, lymphocytes and neutrophils levels when compared to healthy rats (group C) . In the other words the herbal treated rats showed normal values of CBC count after treatments.

Effects of herbs on serum biochemical parameters

Based on biochemical analysis, herbs didn't have any effect on FBS and lipid profile as compared to the control group. Also concentrations of total bilirubin, total protein and albumin in treated sera with all of doses of Jujube are similar to healthy samples (Table 3a). At the same time, the decrease in total protein and albumin levels and the increase in total bilirubin induced by 2000 and 5000 mg/kg Saffron were significantly observed when compared to control (Table 3b).

Effects of herbs on serum hepatic enzymes

Results revealed that treatment with J4, J5, S3, S4 and S5 caused a significant increase ($p < 0.05$ vs controls) in serum concentrations of liver enzymes (Table 4).

Effects of herbs on renal biomarkers

Groups-J5, S4, S2 rats showed a significant ($P < 0.05$) increase in BUN, cratinine and uric acid levels in comparison to control rats. Whereas other treated rats showed normal levels of these factors (Table 5).

Discussion

Recently herbal medicine has attracted great attention and is increasingly applied as alternatives to chemical drugs. Certain factors contributed to their importance including effectiveness, availability, affordability, apparently and safety activities [18]. In spite of great therapeutic ability of herbs they may have side effects in their toxic doses [19]. Therefore, before using any herbal extraction it should be evaluated its toxic effects on various organs of body such as liver, kidney and blood. There have been a few reports on possible toxicological properties of Saffron petals and Jujube fruits [20]. This study aimed to investigate effects of high concentrations of these plants on functions of liver and kidney in rats.

Table 1 The total antioxidant activity, total phenolics and total anthocyanins of both extracts

Antioxidant content	Jujube fruit	Saffron petal
TAA (M Fe(II)/g DW)	350.63 ± 6.25	442 ± 5.87
TPC (GAE/g DW)	210 ±. 2.66	294 ± 3.33
TAC (mg cy-3-glu/l)	504.65 ± 7.12	610.22 ± 8.32

Data are expressed as mean ± SD ($n = 3$)

Table 2 Effects of herbs on body weight of rats

Experimental groups[a]	Body weight change (%)	Experimental groups	Body weight change (%)
Healthy Control	5.63 ± 0.25[b]	Healthy Control	5.63 ± 0.25
J1 (150 mg/kg)	5.85 ± .21	S1(150 mg/kg)	5.79 ± 0.21
J2 (500 mg/kg)	5.65 ± 0.1	S2 (500 mg/kg)	5.65 ± 0.1
J3 (1000 mg/kg)	5.61 ± 0.2	S3 (1000 mg/kg)	5.63 ± 0.2
J4 (2000 mg/kg)	5.65 ± 0.3	S4 (2000 mg/kg)	5.55 ± 0.3
J5 (5000 mg/kg)	5.71 ± .2	S5 (5000 mg/kg)	5.01 ± 0.2*

[a]For details of experimental conditions see the text
[b]Data are expressed as mean ± SD of 8 rats in each group (In each column)
*was considered significant at $P < 0.05$ when compared with the healthy control group

Also the antioxidant properties of aqueous extracts of Jujube and Saffron were evaluated.

A complete picture of total antioxidants capacity of both extracts determined was obtained via analysis by FRAP and Ciocalteu assays. The results showed that the Saffron petals extract has a higher content in total antioxidants and total phenolices than Jujube fruit extract. The anthocyanins amount was also determined by spectrophotometry. It was found that Saffron petals were richer in anthocyanins compared to Jujube fruits.

Liver is a vital organ in body that regulated various metabolic and detoxification pathways. Excretion of most toxicants and their metabolites is by way of the kidneys, So liver or kidney injuries induced by common agents such as drugs or organic components have serious outcomes in body. Various studies were reported

Table 3 Effects of herbs on general biochemical parameters in serum of rats

Experimental groups[a]	Total protein (g/dl)	Albumin (g/dl)	Total bilirubin (mg/dl)
a. Jujube			
Healthy Control	8.68 ± 0.6[b]	4.88 ± 0.7	0.85 ± 0.1
J1 (150 mg/kg)	8.65 ± 0.5	4.91 ± 0.2	0.88 ± 0
J2 (500 mg/kg)	8.63 ± 0.3	4.87 ± 0.4	0.90 ± 0
J3 (1000 mg/kg)	8.62 ± 0.6	4.90 ± 0.2	0.87 ± 0.2
J4 (2000 mg/kg)	8.61 ± 0.8	4.83 ± 0.3	0.91 ± 0.3
J5 (5000 mg/kg)	8.62 ± 0.6	4.81 ± 0.2	0.90 ± 0.3
b. Saffron			
Healthy Control	8.68 ± 0.6[b]	4.88 ± 0.7	0.85 ± 0.1
S1 (150 mg/kg)	8.75 ± 0.4	4.91 ± 0.6	0.84 ± 0.2
S2 (500 mg/kg)	8.59 ± 0.1	4.83 ± 0.4	0.89 ± 0.3
S3 (1000 mg/kg)	8.61 ± 0.5	4.85 ± 0.6	0.91 ± 0.4
S4 (2000 mg/kg)	7.74 ± 0.7*	4.72 ± 0.2*	0.99 ± 0.5*
S5 (5000 mg/kg)	7.52 ± 0.5*	4.59 ± 0.4*	1.08 ± 0.6*

[a]For details of experimental conditions see the text
[b]Data are expressed as mean ± SD of 8 rats in each group (In each column)
*was considered significant at $P < 0.05$ when compared with the healthy control group

Table 4 Effects of herbs on liver enzymes in serum of rats

Experimental groups[a]	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	LDH (IU/L)
a. Jujube				
Healthy Control	81 ± 8[b]	154 ± 11	190 ± 17	354 ± 19
J1 (150 mg/kg)	85 ± 6	152 ± 7	191 ± 16	356 ± 13
J2 (500 mg/kg)	87 ± 7	156 ± 8	196 ± 12	358 ± 19
J3 (1000 mg/kg)	88 ± 9	158 ± 9	199 ± 11	361 ± 12
J4 (2000 mg/kg)	97 ± 7*	167 ± 8*	205 ± 10*	375 ± 19*
J5 (5000 mg/kg)	108 ± 6*	188 ± 11*	217 ± 11*	3.86 ± 10*
b. Saffron				
Healthy Control	81 ± 8[b]	154 ± 11	190 ± 17	354 ± 19
S1 (150 mg/kg)	83 ± 6	156 ± 7	193 ± 11	353 ± 8
S2 (500 mg/kg)	85 ± 9	157 ± 8	196 ± 10	361 ± 9
S3 (1000 mg/kg)	95 ± 7*	165 ± 6*	208 ± 9*	388 ± 10*
S4 (2000 mg/kg)	1.08 ± 10*	178 ± 9*	228 ± 11*	399 ± 12*
S5 (5000 mg/kg)	1.19 ± 11*	195 ± 11*	242 ± 14*	420 ± 16*

[a]For details of experimental conditions see the text
[b]Data are expressed as mean ± SD of 8 rats in each group (In each column)
*was considered significant at $P < 0.05$ when compared with the healthy control group

hepato and nephrotoxicity activities of medicinal plants including Paeonia spp [21], Polygonum multiflorum [22, 23], Teucrium polium L. (400 mg/kg; [24]), Capparis Spinosa (400,800 mg/kg; [25]), Echium amoenum (200 mg/kg; [26]), Melissa officinalis (1350 mg/kg; [27]) Cichorium Intybus (400 mg/kg; [28]).

Our study illustrated that all doses of Saffron and Jujube extracts did not cause mortality in treated rats. A significant reduction of body weight was just observed in S5-treated group (5000 mg/kg) as compared to control group ($P < 0.05$). Our data also indicated that all doses of Jujube treatments (J1–J5) and some doses of Saffron treatments (S1–S3) did not show any significant difference in some biochemical parameters such as FBS, lipid profile, total protein, albumin and total bilirubin. While two higher doses (2000 and 5000 mg/kg) of Saffron caused a remarkable increase in the levels of total total bilirubin and decrease of total protein and albumin levels.

Table 5 Effects of herbs on kidney function

Experimental groups[a]	BUN (mg/dl)	Cratinine (mg/dl)	Uric acid (mg/dl)
a. Jujube			
Healthy Control	21.61 ± 1[b]	0.53 ± 0.06	2.12 ± 0.1
J1 (150 mg/kg)	21.73 ± 2	0.54 ± 0.03	2.23 ± 0.3
J2 (500 mg/kg)	21.98 ± 1	0.53 ± 0.07	2.18 ± 0.5
J3 (1000 mg/kg)	22.11 ± 2	0.54 ± 0.03	2.55 ± 0.4
J4 (2000 mg/kg)	22.20 ± 2	0.57 ± 0.04	2.61 ± 0.15
J5(5000 mg/kg)	22.86 ± 1*	0.61 ± 0.07*	2.85 ± 0.11*
b. Saffron			
Healthy Control	21.61 ± 1	0.53 ± 0.06	2.12 ± 0.1
S1(150 mg/kg)	21.58 ± 2	0.56 ± 0.02	2.25 ± 0.3
S2 (500 mg/kg)	21.62 ± 1	0.57 ± 0.03	2.31 ± 0.3
S3 (1000 mg/kg)	21.64 ± 2	0.59 ± 0.02	2.35 ± 0.2
S4 (2000 mg/kg)	22.46 ± 2*	0.63 ± 0.04*	2.91 ± 0.4*
S5 (5000 mg/kg)	23.16 ± 1*	0.72 ± 0.08*	3.65 ± 0.2*

[a]For details of experimental conditions see the text
[b]Data are expressed as mean ± SD of 8 rats in each group (In each column)
*was considered significant at $P < 0.05$ when compared with the healthy control group

Usually laboratory-based criteria of liver and renal toxicities are explained by ALT and/or ALP and BUN and/or creatinine values, respectively. The increased levels of serum AST, ALT, ALP and LDH enzymes in J4, J5, S3, S4 and S5-treated groups indicated liver dysfunction due to adverse effects of herbs in experimental rats. It may be postulated that high dosages of these extractions especially Saffron petals (5000 mg/kg) caused slight hepatotoxicity. Although previous studies did not reported jujube-induced liver injury, oral administration Saffron petals (160, 320 and 480 mg/kg) after 14 days caused *the elevated* liver enzymes and toxicity in liver [29]. LD50 values of saffron stigma and petal extracts (intra-peritoneal administration) in mice were 1.6 and 6 g/kg [20]. The treatments 75, 150, 225, and 450 mg/kg body weight of saffron petal extract has no significant changes in hematological parameters while the number of white blood cells in treatment groups increased [30]. Although Jujube has various medical applications including anticancer [31], this herb did not show any toxicity.

Renal insufficiency occurred with high levels of BUN, Creatinine and uric acid in treated rats with J5, S4 and S5 extractions. Whereas other treated groups showed normal levels of these factors similar control group. It is highly demanded to study the exact mechanism of these effects of Saffron and Jujube to develop their applications in clinical trials.

Conclusions

Our results clearly showed Saffron petals at 1000, 2000 and 5000 mg/kg doses were more toxic on liver and kidneys that were comparable to Jujube treatments. Further studies on improving the quality and nutritional value of this herbal mixture (Saffron petals and Jujube fruits) are recommended.

Abbreviations

ALP, Alkaline Phosphatase; ALT, Alanine Amino Teransferases; AST, Aspartate Amino Teransferases; BUN, Blood Urea Nitrogen; DLC, Leukocyte Count; FBS, Fasting Blood Suger (FBS); Hb, Hemoglobin; LDH, Lactate Dehydrogenase; PCV, Packed Cell Volume; RBC, Red Blood Cells; WBS, Total White Blood Cells.

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Authors' contributions

RH designed the study, participated in data analysis and manuscript preparation. MH participated in study design and helped in manuscript preparation. BS and RE participated in experiments doing, data analysis and manuscript preparation. All authors read and approved the final manuscript.

Competing interests

Banafsheh Safizadeh, Reyhane Hoshyar, Mina Hemmati, Asghar Zarban and Roshanak Ebrahimi declare that they have no competing interests.

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