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Study the Possible Protective Effect of Saffron Extract on Induced Rats Toxicity by Acrylamide

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Abstract

Acrylamide is a dietary pollutant in a variety of commonly eaten food product, and been attributed to liver and kidney damage. Some researchers suggest that saffron, and its active constituents may have preventive properties against digestive and urinary tract disorders. The purpose of this research was to examine the possible protective benefits of saffron extract against kidney and liver damage of rats produced by acrylamide.Six groups of five rats, each one of them was left on basal diet as negative control, the 2nd group received acrylamide and kept as positive control, the other groups received acrylamide; and vitamin C or saffron, or saffron and vitamin C.Rats that received orally acrylamide (1.2 µg/kg/day) and at the same time, saffron extract (200 mg/kg) + (75 mg/ daily) of vitamin C, levels of creatinine and urea, protein fractions, and serum minerals were significantly high (P<0.0001).But the rats orally given acrylamide (1.2 µg/kg/day), and after one hour were given saffron extract (200 mg/kg) + (75 mg/daily) of vitamin C, their liver functions tests and minerals were still significantly high (P<0.0001). In contrast to the control groups, vitamin C and saffron extract could reverse these alterations in the rats (P<0.05).

Keywords: Saffron extract; Acrylamide; Liver; Kidneys; Vitamin C.

Introduction

*Saffron (Crocus sativus), a member of the Iridaceae family, is a well-known flavoring and coloring product in the culinary business.The pharmaceutical sector is interested in the pharmacological effects of saffron.*The saffron extract contains the active compounds crocetin, crocin, safranal, and picrocrocin ***(El Midaoui et al., 2022)***.*The pharmacological effects of saffron include anticancer, anti-depressive, anti-tremor, and anticonvulsant properties. Saffron is a widely appreciated medicinal herb* ***(Hariri et al., 2018)****, utilized for dietary and therapeutic purposes, in the food business (herbal and flavoring agents), and in the textile industry (dyes).*Moreover, its golden yellow-orange hue is mostly attributed to the existence of α-crocin.Active metabolites contained in saffron, like crocetin, crocin, safranal, and picrocrocin, are responsible for saffron's therapeutic properties. These active metabolites have anticonvulsant, antihypertensive, antitussive, antidepressant, anxiolytic, antinociceptive, antigenotoxic, antioxidant, aphrodisiac, anti-inflammatory, anticancer, and muscle relaxant properties ***(Attia et al., 2021)***.Saffron includes non-volatile and volatile chemicals that are beneficial for treating a variety of ailments ***(Singh and Sharma, 2020)***.The phytochemicals of saffron have been reported to show beneficial effects against numerous diseases, such as diabetes, neurodegenerative diseases, cognitive problems, depression, inflammatory diseases, autoimmune diseases, digestive diseases, and cardiovascular inflammations ***(Kabir et al., 2022)***.Liver comprise

nearly 2% of an individual's total mass is comprised of the liver. Hepatic cells are the primary parenchymal cells and are accountable for a significant amount of the liver's functionality ***(Campana et al., 2021)***.However, fatalities due to liver pathology are counted by millions because of several diseases, cirrhosis is the largest reason for mortality worldwide followed by carcinoma **(*Asraniet al .,2019)***.

The kidneys are intricate structures that are essential for regular human activity. A considerable portion of a person's survival depends on the kidneys' critical operations and activities.Renal problems may occur at any age and to anybody***(Bowdino et al., 2022)***.Renal disease is a condition defined by impairment of the kidney's glomerular filtration rate and identified by the increase of final metabolites of nitrogen (creatin ine and urea) ***(Kellumet al., 2021)***.

Acrylamide (ACR) is a dietary pollutant found in a variety of commonly eaten food products, making individuals exposed to this toxin. Nevertheless, there has been some progress in attempts to limit the development of acrylamide in diet. The Maillard reaction is the first practical method that may be regulated to limit acrylamide synthesis. Acrylamide formation in foods is mostly tied to the Maillard process. In addition, altering the processing parameters, like the heating process's temperature and length, and incorporating specific preheating procedures, like blanching and soaking, may further limit the development of acrylamide ***(Rifai and Saleh 2020,)***.This study is for investigating the possible preventive benefits of saffron and its bioactive components on acrylamide-induced kidney and liver damage in rats.

Materials and methods

Materials:

Plant samples: Saffron was purchased from Surour herbal Co., Tanta -Gharbia – Egypt.

Acrylamide: Purchased from Sigma Pharmaceutical Industries, Egypt (SAE).

Animals: Thirty male Sprague Dawley rats, 150±5g, were obtained from Serum and Vaccine Center, Cairo, Egypt. The rats are 5 weeks old.

Diet:

The basic diet is as indicated by***(Ain 1993)*** as follows: corn oil (10%), protein (10%), vitamin mixture (1%), mineral mixture (4%), cellulose (5%), methionine (0.3%), choline chloride (0.2%), and corn starch (69.5%). The utilized vitamins and salt mixtures components were formulated according to ***(Campbell, 1963)*** and ***(Hegstedet al.,1941)***, respectively.

Methods:

Preparation of saffron:

Using a percolation technique and a concentration of 80% (v/v), the hydroalcoholic extract was produced. Employing a vacuum rotary evaporator (Hiedolph, Germany), the extract was concentrated and then dried in a desiccator.The extract yield (w/w) was determined as the weight of dry extract divided by the weight of dry precursor material multiplied by 100. Using the HPLC technique, the crocin concentration of the hydroalcoholic extract of saffron was determined ***(Reddy et al., 2020).***

HPLC conditions: Utilizing high-density chromatography, the phenolic components of Crocus sativus extract were identified. At the National Research Center in Cairo, an Agilent 1260 series was used for HPLC analysis. Employing the Eclipse C18 column (4.6 mm x 250 mm i.d., 5 µm), the separation was performed. The mobile phase at a flow rate of 1 ml/min consisted of water (A) and 0.05% trifluoroacetic acid in acetonitrile (B) in water. The mobile phase was successively adjusted in a linear gradient as described below: 0 min (82% A); 0 - 5 min (80% A); 5 - 8 min (60% A); 8 – 12min (60% A); 12 - 15 min (82% A); 15 - 16 min (82% A)and 16 - 20 (82%A). The 280 nm wavelength was used to monitor the performance of the multi-wavelength detector.Every sample solution was injected at a volume of 5 µl.The column was retained at 40 degrees centigrade.

Table (1)

Chromatographic analysis of the principal bioactive constituents in saffron by HPLC connected to the mass detector in ESI+ and ESI-

RT (Minutes)	Compound	Maximum UV-Vis (nm)	ESI+ (m/z)	ESI− (m/z)
7.5	Picrocrocin	250	510.5; 364.3; 352.3; 336.2; 328.3; 183.7; 157.8; 150.5; 122.6; 80.9	1481.3; 666.7; 516.8; 386.0; 182.2; 152.7
11.6	Kaempferol diglucoside	265; 348	632.9; 346.7	610.0; 283.7
21.9	*trans*-crocin-4	262; 322; 440; 465	998.9; 674.6; 510.4; 348.1	1335.8; 650.6; 327.0; 282.9
27.7	*trans*-crocin-3	260; 324; 441; 460	836.6	
31.7	*trans*-crocin-2′	260; 327; 441; 465	674.7; 594.0; 514.1; 350.9; 131.1; 103.2; 73.1	
34.3	Safranal	312	—	—
35.9	*cis*-crocin-4	226; 261; 324; 432; 455	999.3; 820.5; 669.3; 610.7; 390.0; 348.0	650.6
38.5	*trans*-crocin-2	261; 321; 432; 459	676.1; 540.6	652.2; 328.1; 312.1; 282.1

***UV-Vis**:Ultraviolet-visible-near infrared Spectrophotometry.**ESI:**Electrospray ionization .*

N.B:The values in italics show molecular fractional overlaps acquired from ***(Hollebeeck et al.,2013)***.

Experimental design: Rats were housed separately in stainless steel containers at around 55% of relative humidity and a temperature of 25 ± 2ºC with unrestricted access to both water and food.After the adaptation period; ***(Abhari et al., 2016)***,rats were separated into 6 groups, 5 rats each; groups receiving the basal diet for the whole period (28 days) as follows:

a. **(-ve) group:** fed on basal diet only.

b. **(+ve) group:** received acrylamide only orally (1.2 µg/kg/day, dissolved in distilled water).

c. **Group (1):**was orally given acrylamide (1.2 µg/ kg/day) and, at the same time, saffron extract (200 mg/kgbody wt.).

d. **Group (2):**was orally given acrylamide (1.2 µg/kg/day) and, at the same time,(75 mg/day) of vitamin C.

e. **Group (3):** was orally given acrylamide (1.2 µg/kg/day) and, at the same time, saffron extract (200 mg/kg body wt.) + (75 mg/day) of vitamin C.

f. **Group (4):**was orally given acrylamide (1.2 µg/kg/day) and, after one hour, saffron extract (200 mg/kg body wt.) + (75 mg/day) of vitamin C.

Chemical analysis:

After the experimental period (4 weeks), rats were starved overnight prior to sacrifice. Blood specimens were obtained from every rat's hepatic portal vein and centrifuged for a ten-minute period at 3000 rpm to separate serum.Before the analysis, serum was thoroughly isolated, transferred to dry pure Eppendorf tubes, and stored at -20 degrees centigrade.The liver was disse cted and rinsed with isotonic saline, cleaned with filter paper, and then separated into two sections. The first portion was preserved in 10% formalin saline for histological analysis ***(Loha et al., 2019)***;The second portion was stored at -80 degrees centigrade for tissue homogenate preparation to determine liver mineral content. 20 minutes were spent centrifuging the homogenate at 10.000 rpm.Furthermore, serum aspartate aminotransferase (AST) and alanine aminotransferase(ALT)concentrations were measured using the technique outlined in ***(Reitman and Frankel, 1957)***.The colorimetric approach adopted by ***(Roy, 1970)***was employed to evaluate serum *alkaline phosphatase* (ALP) levels.The serum protein fractions (total protein, albumin, and globulin) were determined according to ***(Gornall et al., 1949)***. Total bilirubin and direct bilirubin were determined according to ***(Garber, 1981)***.Renal functions (uric acid, creatinine and urea)were described by***(Palmiere and Mangin, 2015)***.The liver and kidneys of rats in each group were collected, cleaned and weighed***(Park et al., 2000)***. Determination of minerals in liver tissues ***(Abukunna, 2008).*** Determination of renal tissue Na^{+}, K^{+}, Ca^{++} and P^{+++} by ***(Hillis, 1971).*** Determination of serum minerals according to***(ERASLAN, 2002).***

Histopathology investigation:

Immediately after removing the organs from rats, the kidneys and liver were preserved in 10% buffered neutral formalin. Following fixation, samples were prepared for histopathology investigations***(Liu-Guan et al., 2022).***

Statistical analysis:

All data were presented as the mean, standard error of the mean ± SEM. A one-way ANOVA was employed to test the means,at $P < 0.05$, the results were deemed statistically significant***(Morgan and Griego, 1998)***.

Results and discussion

Impact of saffrom (*Crocus sativus)* on liver functions in rats (table 2):

It was obvious that orally ingested acrylamide induced a substantial rise ($P \leq 0.05$) in the concentrations of alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase(AST)in comparison to the normal control group.It's clear that aspartate aminotransferase (AST)for control (+ve) was higher than control (-ve) and all the other groups.The table shows that aspartate aminotransferase(AST) in all groups were lower values compared with control (+ve),with the fact that G_1, G_3,and G_4were highly significant different ($P<0.001$) compared to control (+ve), and choose to the control (-ve) $G_2$was significantly different ($P<0.01$) compared to control

(+ve).alanine aminotransferase (ALT) and alkaline phosphatase (ALP)behaved in the same way; this means that G_3 and G_4 gave the better result.

According to ***Harchegani et al.,(2019)***,in a dose-dependent manner, the saffron extract reduced the concentrations of liver enzymes. This finding explains that saffron extract had hepatoprotective properties towards the damage produced by acrylamide. In prior research, the preventive effect of saffron against hepatocellular carcinoma was also explored. In mice, subacute acrylamide intake modifies enzymatic, biochemical, and hematological indices and promotes genotoxicity. ***(Bostan et al., 2017)*** found that vitamin C and large dosages of aqueous saffron extract partly diminished acrylamide toxicity; nevertheless, these treatments didn't lessen acrylamide's genotoxic effect.

Table (2)

Effect of saffron on liver functions in rats

Groups	AST (U/L)	ALT (U/L)	ALP(U/L)
	Mean ± SE	Mean ± SE	Mean ± SE
(-ve)	110.00±3.21^{d}	33.00±1.53^{d}	104.33±6.57^{d}
(+ve)	264.00±3.78^{a}	86.33±2.03^{a}	264.00±3.78^{a}
G1	116.00±2.31^{c}	45.00±1.73^{b}	118.67±1.76^{c}
G2	120.33±3.28^{b}	52.33±1.45^{b}	124.67±2.03^{b}
G3	112.00±1.15^{c}	34.67±1.76^{c}	107.67±5.04^{d}
G4	114.33±2.33^{c}	37.00±1.15^{c}	114.33±2.40^{c}

a=*p < 0 .05;* ***b=*****p < 0.01and* ***c=******* P < 0.001*

Effect of saffron(*Crocus sativus)* on protein fractions in rats (table 3):

The outcome of this study can be summarized in Table 3. With reference to total protein (TP)in the (-ve) group was 5.33±0.32, which is considered normal, while the control positive showed double reading of the control negative. The other groups, the level of total protein (TP) showed lower levels and G4 was the lowest but didn't reach the control (-ve), however the decrease is highly significant (P < 0.001).This result is agreeable with ***Gholamnezhad et al.,(2013)***.They stated that on several inflammatory disorders, *C. sativus* and its components had been demonstrated to have an anti-inflammatory impact.The protective impact of *Crocus sativus* extract and safranal on markers of inflammation in sensitized guinea pigs was investigated by***Alaa and Munaf, (2021).***The findings indicated that the blood levels of total protein (TP) were higher in sensitized animals than in control animals. Administration of sensitized pigs with the extract of *Crocus sativus* inhibited the elevation of serum total protein (TP) concentrations.

Albumin (ALB) and globulin (GLB) levels in blood followed the same behavior as total blood protein.All groups were lower than the control (+ve) with high significant difference(P<0.001) compared to control (+ve). ***(Kanakis et al., 2007)*** analyzed the association between safranal and human serum albumin, and their findings demonstrated that safranal attaches nonspecifically (H-bonding) through polar protein groups with a binding constant of K_{saf} = 2.11 (±0.35) × 10^3 M^{-1}. At lower ligand concentrations (1 μM), there were no changes to the secondary structure of proteins, but at greater concentrations, alterations were found (1 mM).

Evaluation of the total protein (TP) , albumin(ALB), and globulin(GLB) levels reflects the actual functioning of an organism ***(Santamaria-Kisiel et al., 2006)(Yılmaz et al., 2003)***.This study is consistent with a number of earlier studies that investigated the change in blood protein composition of glioma patients***(Hamad et al., 2009)*** and pulmonary tumor patients***(Gao et al., 2005)***. In this trial, a 28-day therapy with saffron extract (200 mg/kg) and vitamin C (75 mg/day) restored blood protein levels to near-normal levels.

Table (3)

Effect of saffron on (Crocus sativus) on total protein and fractions

Groups	TP (g/dl)	ALB(g/dl)	GLB(mg/dl)
	Mean ± SE	Mean ± SE	Mean ± SE
(-ve)	5.34±0.32^{d}	3.77±0.15^{c}	1.57±0.19^{d}
(+ve)	10.70±0.72^{a}	6.40±0.32^{a}	4.30±0.40^{a}
G1	7.23±0.21^{b}	4.53±0.18^{b}	2.70±0.12^{c}
G2	6.83±0.18^{c}	4.63±0.33^{b}	3.07±0.15^{b}
G3	6.04±0.23^{c}	3.87±0.22^{c}	2.17±0.12^{c}
G4	6.70±0.29^{c}	4.33±0.09^{b}	2.37±0.24^{c}

a=*p < 0 .05; **b=****p < 0.01and **c=**** P < 0.001*

Effect of saffron on total bilirubin and direct bilirubin in rats (table 4):

The results in table (4) can be summarized as follows: G_3 and G_4 are the groups that have effects in decreasing the levels of total bilirubin and direct bilirubin.These groups are the ones which rats were given acrylamide with saffron and vitamin C whether together or after one hour.All groups were lower than the control (+ve), but G1, G2, G3, and G4 displayed high significant differences (P<0.01) compared to the control (+ve).All groups were lower than the control (+ve), while G_3 and G_4displayed the highest significant difference (P<0.001) compared to the control (+ve), while G_1 and G_2 showed significant differences (P<0.01) compared to the control (+ve).However, ***Hariri et al.,(2018)***report that ACR, vitamin C and saffron didn't change serum total and direct bilirubin levels significantly.The intake of saffron was related to reduced concentrations of aspartate aminotransferase(AST), alanine aminotransferase(ALT), and bilirubin***(Omidi et al., 2014)***.

These results are in accordance with this study, which showed that saffron extract lowered the average levels of alanine aminotransferase(ALT), aspartate aminotransferase(AST), alkaline phosphatase (ALP), and bilirubin.Total bilirubin is one of the most reliable tests for liver function as it indicates the liver's capacity to absorb and convert bilirubin into bile***(Arias, 2012)***. Usual amounts of albumin and total protein are related to healthy liver functioning ***(Barle et al.,2006)***. In our study, the blood levels of total protein and albumin were significantly increased by *Crocus sativus*. According to our findings, the treatment of *C. sativus* extract (200 mg/kg) and vitamin C (75 mg/day) almost restored the increased levels of blood enzymes of acrylamide to normal values.

Table (4)

Effect of Saffron on total bilirubin and direct bilirubin

Groups	Total bilirubin(mg/dl)	Direct bilirubin(U/L)
	Mean ± SE	Mean ± SE
(-ve)	0.23±0.01^{b}	0.11±0.01^{d}
(+ve)	1.77±0.15^{a}	1.03±0.15^{a}
G1	0.28±0.01^{b}	0.18±0.01^{b}
G2	0.31±0.02^{b}	0.22±0.02^{b}
G3	0.24±0.02^{b}	0.14±0.01^{d}
G4	0.26±0.01^{b}	0.15±0.02^{c}

a=*p < 0 .05; **b=****p < 0.01and **c=**** P < 0.001*

Effect of *Crocus sativus* on renal functions for rats (table 5):

Results in table (5) indicated that the creatinine in the normal rats was 0.86±0.01, while in the positive group was 1.73±0.12. It's clear that creatinine for the control (-ve) was lower than the control (+ve). Other groups G_1, G_2, G_3 and G_4,were 1.01±0.05, 1.02±0.09, 0.89±0.03,and 0.94±0.02,respectively; G_3 and G_4 were lower than the control (+ve). G_3 showed a high significant difference (P<0.001) compared to the control (+ve), but $G_1$and G_2showed highly significant differences (P<0.01) compared to the control (+ve). As for urea in the control (-ve) group, it was 12.33 ± 1.45, while in the control (+ve) group, it was 32.33±1.44. It's clear that urea for control (+ve) was higher than control (-ve) and other groups;14.00±0.58, 11.00±1.15, 12.67±1.76,and 13.00±1.73,respectively. All groups were lower than the control (+ve). G_3 displayed a high significant difference compared to (+ve). With regard to the uric acid in the (-ve) group, it was 0.20±0.06, while in the (+ve) group was 2.43±0.29. It's clear that uric acid for control (+ve) was higher than control (-ve) and other groups;1.10±0.23, 0.97±0.12, 0.33±0.09,and 0.40±0.12,respectively. All groups were lower than the control (+ve), but G_4 revealed a high significant difference (P<0.001)compared to the control (+ve).For 28 days, 100 or 200 mg/kg of the saffron extract was administered orally to STZ-diabetic mice. STZ elevated concentrations of urine volume, fasting blood glucose(FBS), creatinine (Cr), and blood urea nitrogen(BUN). The extract at a dosage of 200 mg/kg lowered FBS, whereas both concentrations suppressed urine volume, BUN, and Cr levels. Our study agreed with these results, according to ***(Hosseini et al., 2018)***.

Table (5)

Effect of *Crocus sativus* on renal functions of rats

Groups	Creatinine(g/dl)	Urea(g/dl)	Uric acid(g/dl)
	Mean ± SE	Mean ± SE	Mean ± SE
(-ve)	0.86±0.01^{c}	12.33±1.45^{c}	0.20±0.06^{d}
(+ve)	1.73±0.12^{a}	32.33±1.44^{a}	2.43±0.29^{a}
G1	1.01±0.05^{b}	14.00±0.58^{b}	1.10±0.23^{b}
G2	1.02±0.09^{b}	11.00±1.15^{d}	0.97±0.12^{b}
G3	0.89±0.03^{c}	12.67±1.76^{c}	0.33±0.09^{cd}
G4	0.94±0.02^{d}	13.00±1.73^{b}	0.40±0.12^{c}

a=*p < 0 .05; **b=****p < 0.01 and **c=**** P < 0.001*

Effect of *Crocus sativus* on liver and kidneys weight (table 6):

The positive control group had an increase in liver and kidney weights compared to the negative control group. Liver and kidney weight showed a significant decrease in all treated groups compared to the positive control. The best results were found in group 3 where saffron extract in (200 mg/kg) + vitamin C (75 mg/daily) because these treatments showed a significant decrease compared to other treated groups, as shown in Table 6.Extract of *Crocus sativus* and its combination showed significantly increased relative weights of kidneys. The relative weights of the liver were significantly increased in rats that were treated with the saffron extract (200 mg/kg body wt.).Our findings were agreeable with ***(Ramadan et al., 2012)*** and ***(Mokbll et al., 2020)***.

Table (6)

Effect of *Crocus sativus* on liver and kidneys weight

Groups	Liver weight%	Kidneys weight%
	Mean ± SE	Mean ± SE
(-ve)	2.31±0.03^{d}	2.03±0.04^{d}
(+ve)	3.74±0.02^{a}	3.14±0.02^{a}
G1	3.01±0.05^{a}	2.98±0.03^{b}
G2	2.51±0.03^{c}	2.63±0.04^{b}
G3	2.35±0.01^{bc}	2.18±0.03^{c}
G4	2.87±0.04^{b}	2.34±0.01^{bc}

a=*p < 0 .05; **b=****p < 0.01 and **c=**** P < 0.001*

Effect of *Crocus sativus* on serum minerals for rats (table 7):

The results revealed that the mean value of serum Na^{+}, K^{+}, Ca^{++},andP^{+++} in the rats in the group (+Ve) was significantly increased compared with the (-ve) group.At the same time, all treated groups recorded a significant decrease in comparison to the control (+Ve). The lowest level of serum Na^{+}, K^{+}, Ca^{++},and P^{+++} was recorded by group 3.These results agreed with ***(Saleem et al., 2006)***. The result of this study showed that the effect of the extract of saffron at the highest dose might be due to the diuretic effect of this plant, which is agreeable with ***(Imenshahidi et al., 2013)*** and ***(Modaghegh et al., 2008).***

Table (7)

Effect of *Crocus sativus* on serum minerals of rats

Groups	Serum Na^{+} (g/dl)	Serum K^{+} (g/dl)	Serum Ca^{++} (g/dl)	Serum P^{+++} (mg/dl)
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
(-Ve)	121.00±2.08^{c}	4.50±0.32^{d}	8.13±0.20^{c}	6.30±0.12^{c}
(+Ve)	144.33±1.86^{a}	7.07±0.34^{a}	11.07±0.26^{a}	8.50±0.11^{a}
G1	130.00±1.15^{b}	6.10±0.17^{b}	9.57±0.15^{b}	6.93±0.24^{c}
G2	131.33±2.33^{b}	5.80±0.23^{c}	9.10±0.12^{b}	7.33±0.15^{b}
G3	124.00±2.08^{c}	5.33±0.12^{c}	8.43±0.27^{c}	6.47±0.38^{c}
G4	127.67±2.60^{b}	5.60±0.17^{c}	9.20±0.17^{b}	5.63±0.14^{d}

a=*p < 0 .05; **b=****p < 0.01 and **c=**** P < 0.001*

Effect of *Crocus sativus* on liver Na^{+}, K^{+}, Ca^{++}, and P^{+++} for rats (table 8):

The mean values of liver Na^{+}, K^{+}, Ca^{++},and P^{+++} were significantly decreased in the (+ve) control rats compared to the (-ve) control group. All treated groups showed a significant increase ($P<0.05$) compared with the (+ve) control rats. The best result was obtained in G3 and G4 rats.The result of this study agreed with that of ***Saleem et al.,(2006).*** The effect of the extract of saffron at the high dose may be due to its diuretic effect, that's agreeable with ***(Imenshahidi et al., 2013)*** and ***(Modaghegh et al., 2008).***

Table (8)
Effect of saffron on liver Na^{+}, K^{+}, Ca^{++},and P^{+++} of rats

Groups	Na^{+} (mg/l)	K^{+} (mg/l)	Ca^{++} (mg/l)	P^{+++} (mg/l)
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
(-ve)	72.33±1.76^{a}	2.17±0.02^{b}	1.54±0.06^{ab}	6.99±0.07^{b}
(+ve)	53.32±3.18^{c}	1.30±0.12^{c}	0.82±0.02^{c}	5.76±0.03^{c}
G1	50.00±3.21^{c}	1.95±0.08^{c}	1.15±0.02^{b}	6.12±0.04^{b}
G2	67.00±2.31^{b}	2.10±0.03^{b}	0.97±0.03^{c}	5.91±0.02^{c}
G3	69.67±1.45^{b}	2.21±0.02^{b}	1.79±0.02^{a}	7.30±0.01^{a}
G4	69.30±2.96^{b}	2.75±0.03^{a}	1.83±0.04^{a}	7.54±0.03^{a}

a=**p < 0 .05; **b=**p < 0.01 and **c=* P < 0.001*

Effect of *Crocus sativus* on kidney Na^{+}, K^{+}, Ca^{++},and P^{+++} of rats (table 9):

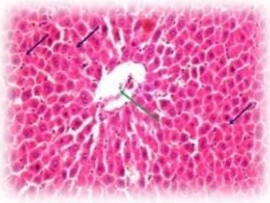
Table 9 showed that the positive control group recorded a significant decrease in the mean value of kidney Na^{+}, K^{+}, Ca^{++}, and P^{+++}compared with the negative control group, while all treatment groups showed a significant increase of these minerals compared with the positive control group. The best results were found in groups treated with the saffron extract and vitamin C. The findings were in agreement with ***(Saleem et al., 2006)***. The study might be attributed to the diuretic effect of saffron, that's agreeable with ***(Imenshahidi et al., 2013)*** and ***(Modaghegh et al., 2008)***.

Table (9)
Effect of saffron on kidney Na^{+}, K^{+}, Ca^{++},and P^{+++} of rats

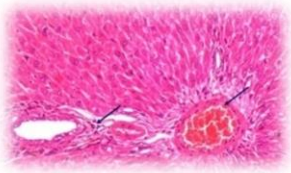
Groups	Na^{+} (mg/l)	K^{+} (mg/l)	Ca^{++} (mg/l)	P^{+++} (mg/l)
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
(-ve)	155.32±1.45^{b}	5.72±0.06^{a}	9.42±0.05^{a}	5.75±0.05^{a}
(+ve)	131.67±2.33^{c}	3.75±0.12^{c}	5.92±0.02^{d}	3.89±0.04^{c}
G1	160.65±2.96^{a}	4.34±0.03^{b}	7.25±0.03^{c}	4.80±0.03^{b}
G2	165.00±3.79^{a}	4.39±0.03^{b}	6.57±0.04^{bc}	4.58±0.29^{b}
G3	158.32±2.60^{b}	5.49±0.04^{a}	9.76±0.02^{a}	5.15±0.03^{a}
G4	151.00±2.51^{b}	4.98±0.09^{b}	8.82±0.04^{b}	4.29±0.04^{b}

a=**p < 0 .05; **b=**p < 0.01 and **c=* P < 0.001*

Histopathological findings of the liver



Photo(1):
A section of the normal liver of (-ve) group showing a central vein (green arrow) surrounded by normal-sized cords of hepatocytes (blue arrows) (H&E X 100).



Photo(2):
A section of the normal liver of (-ve) groups howing a portal tract formed of the mild dilated portal vein, portal arteriole and bile ductules (blue arrows) (H&EX 100).

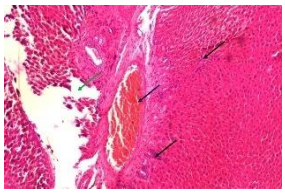


Photo (3):
A Section of intoxicated liver (+ve) group showed dilated marked congested portal venule (blue arrow) surrounded by many chronic inflammatory cells (black arrow) and damaged areas of hepatocytes (green arrow) (H&E X 40).

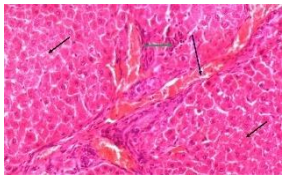


Photo (4):
Higher magnification of intoxicated liver (+ve) group (positive control) showed dilated congested portal venule (blue arrow) surrounded by chronic inflammatory cells (green arrow) surrounded by degenerated hepatocytes (black arrows) (H&E X 100).

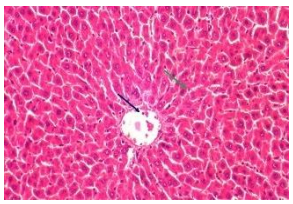


Photo (5):
A Section of normal liver group (1)(was orally administered with acrylamide (1.2 µg/ kg/ day) and, at the same time, saffron extract (200 mg/ kg body wt.), showed normal sized central vein (blue arrow) surrounded by normal sized cords of hepatocytes (green arrow) (H&E X 100).

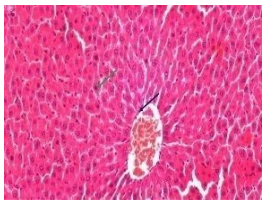


Photo (6):
A Section of normal liver group (2) (was orally administered with acrylamide (1.2 µg/ kg/ day) and, at the same time, (75 mg/ day) of vitamin C), showed normal sized central vein (blue arrow) surrounded by normal sized cords of hepatocytes (green arrow) (H&E X 100).

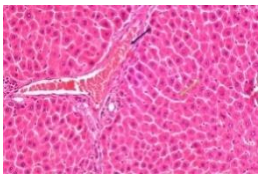


Photo (7):
A Section of liver group (3) (was orally administered with acrylamide (1.2 µg/ kg/ day) and, at the same time, saffron extract (200 mg/ kg body wt.) + (75 mg/ day) of vitamin C), showed mild congested portal venule (blue arrow) surrounded by normal sized with no degeneration or inflammation (green arrow) (H&E X 100).

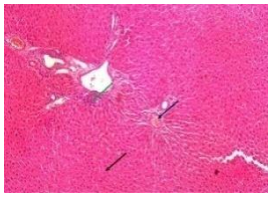


Photo (8):
A Section of liver group (4) **(**was orally administered with acrylamide (1.2 µg/ kg/ day) and, after one hour, saffron extract (200 mg/ kg body wt.) + (75 mg/ day) of vitamin C), showed mild congested central vein (blue arrow) and portal tract surrounded by mild infiltrate of chronic inflammatory cells (green arrow) and normal sized hepatocytes without degeneration (black arrow) (H&E X 40).

Acrylamide is a newly discovered industrial neurotoxin that is neurotoxic to humans and animals. It is present in meals that are heavy in carbohydrates and cooked at high temperatures ***(Mannaa et al., 2006)***. PC12 cells were used to test the impact of crocin on the cytotoxicity produced by ACR. Pretreatment of cells with 10-50 μM crocin substantially and dose-dependently reduced ACR cytotoxicity.In treated cells, crocin prevented the down regulation of Bcl-2 and the upregulation of Bax and lowered apoptosis. Additionally, crocin reduced ROS production in ACR-exposed cells***(Mehri et al.*, 2012)**.Although this study evaluated the preventive effect of saffron extract and its main bioactive constituent, crocin, in rats with acrylamide-induced cancer, nevertheless, related investigations ***(Bandegi et al., 2014), (Rahbani et al., 2012)***, and ***(Amin et al., 2011)***corroborate this study's conclusion that saffron is a promising nutraceutical for preserving liver tissue as shown in photos from (1 – 8).

Histopathological findings of the kidney

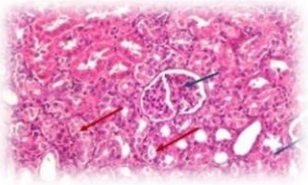


Photo (9):
A section of the normal kidney of (-ve) group showin gaverage-sized glomeruli (blue arrows) surrounded by average-sized tubules lined with cuboidal epithelium (red arrows) (H&E X 100).

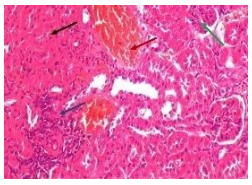


Photo (10):
A Section of intoxicated kidney (+ve) group showed atrophic hyalinized glomerulus (green arrow) surrounded by degenerated fibrotic tubules (black arrow), besides some areas showed chronic inflammation (blue arrow) and others showed congestion (red arrow) (H&E X 100).

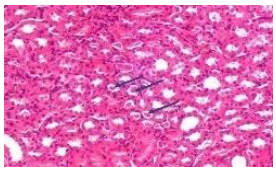


Photo (11):
A Section of intoxicated kidney (+ve) group showed many renal tubules containing colloid casts (blue arrows) (H&E X 100).

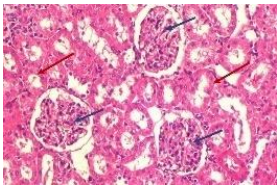


Photo (12):

A Section of normal kidney group (1) (was orally administered with acrylamide (1.2 µg/ kg/ day) and, at the same time, saffron extract (200 mg/ kg body wt.), showed average sized glomeruli with increased number (blue arrows) surrounded by .average sized tubules lined with cuboidal epithelium (red arrows) (H&E X 100)

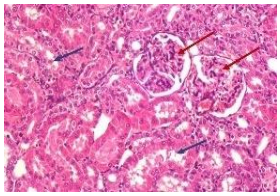


Photo (13):

A Section of normal kidney group (2) (was orally administered with acrylamide (1.2 µg/ kg/ day) and, at the same time, (75 mg/ day) of vitamin C), showed average sized glomeruli (red arrows) surrounded by average sized tubules lined with cuboidal epithelium (blue arrows) (H&E X 100).

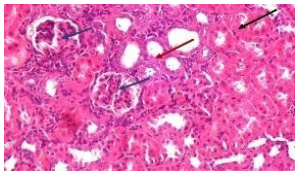


Photo (14):

A Section of kidney group (3) (was orally administered with acrylamide (1.2 µg/ kg/ day) and, at the same time, saffron extract (200 mg/ kg body wt.) + (75 mg/ day) of vitamin C), showed average sized glomeruli (blue arrow) surrounded by average sized renal tubules (red arrow) . with focal area of degeneration (black arrow) and no congestion (H&E X 100)

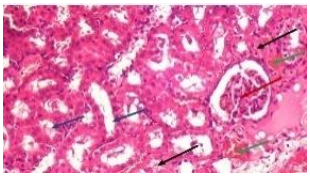


Photo (15):

A Section of kidney group (4) **(**was orally administered with acrylamide (1.2 µg/ kg/ day) and, after one hour, saffron extract (200 mg/ kg body wt.) + (75 mg/ day) of vitamin C), showing average sized glomeruli (red arrow) surrounded by average sized tubules (blue arrows) with focal area of degeneration (black arrows) and foci of congestion (green arrows) (H&E X 100).

Based on the findings of this investigation, the extract prevented nephropathy **(*Hosseini et al., 2018)***.*In addition to its hepatoprotective properties, multiple studies have shown saffron's protective impact on a variety of other tissues* like the kidney***(Hosseinzadeh et al., 2005),*** brain***(Berger et al., 2011)***, and skin***(Das et al., 2004)***vs. a broad variety of chemical substances.Consequently, these outcomes support that by inhibiting oxidative stress, saffron may protect the liver from acrylamide damage as shown in photos from (9 – 15).

Conclusion

These findings imply that saffron and its active ingredient may protect against chronic and acute acrylamide-induced liver and kidney damage. Furthermore, these chemicals may be effective in the fight against toxicity.The preventive qualities of saffron and its compounds against toxicities generated by natural or synthetic toxins, such as acrylamide, have been demonstrated. Additionally, it demonstrated antioxidant action and decreased oxidative damage in several organs, including the kidney, skeletal muscles, and the heart. It has been proposed that the antioxidant properties of saffron components help shield DNA and RNA from damaging pollutants.

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دراسة التأثير الوقائي المحتمل لمستخلص الزعفران على سمية الجرذان المصابة بواسطة مادة الأكريلاميد

ساره محمود مصطفى عمر

مدرس بقسم التغذية وعلوم الأطعمة ، كلية الاقتصاد المنزلي ، جامعة الأزهر ، مصر.

الملخص العربى

مادة الأكريلاميد هي ملوث غذائي يوجد في مجموعة متنوعة من المنتجات الغذائية التي يتم تناولها بشكل شائع ، ويرجع إليه تلف الكبد والكلى. يرى بعض الباحثين أن الزعفران ومكوناته النشطة قد يكون له خصائص وقائية ضد اضطرابات الجهاز الهضمي والمسالك البولية. تتناول الدراسة الحالية الفوائد الوقائية المحتملة لمستخلص الزعفران ضد تلف الكلى والكبد للفئران المستحث بالأكريلاميد فى ذكور الجرذان البيضاء. تم تقسيم الجرذان إلى ست مجموعات متساوية خمس جرذان فى كل مجموعة ، المجموعة الأولى تم تغذيتها على الغذاء الأساسي كمجموعة ضابطة سلبية .المجموعة الثانية تلقت مادة الأكريلاميد وتم الاحتفاظ بها كمجموعة ضابطة إيجابية ، تلقت المجموعات الأخرى مادة الأكريلاميد. وفيتامين ج أو الزعفران أو الزعفران وفيتامين سي.الفئران التي تناولت مادة الأكريلاميد عن طريق الفم (1.2 ميكروجرام / كجم / يوم) وفي نفس الوقت مستخلص الزعفران (200 مجم / كجم) + (75 مجم / يوميًا) من فيتامين سي ، أظهرت النتائج أن إعطاء الأكريلاميد وحده زاد من وزن الكبد والكلى، وارتفعت كلا من إنزيمات الكبد ووظائف الكلى. بينما كانت النتائج في الفئران التي تناولت مادة الأكريلاميد عن طريق الفم (1.2 ميكروجرام/ كجم/ يوم) وفي نفس الوقت مستخلص الزعفران (200 مجم/ كجم) + (75 مجم/ يومياً) من فيتامين C ومستويات الكرياتينين واليوريا ومشتقات البروتين وكانت معادن المصل أعلى معنوياً ($P< 0.0001$) فى حين أن الفئران التى تناولت مادة الأكريلاميد عن طريق الفم (1.2 ميكروجرام/ كجم/ يوم) ثم بعد ساعة واحدة تناولت خلاصة الزعفران (200 مجم/ كجم) + (75 مجم/ يوم) من فيتامين C، كما كانت نتائج مستويات وظائف الكبد والمعادن الكلوية أعلى بشكل ملحوظ ($P< 0.0001$) على عكس المجموعات الضابطة، يمكن لفيتامين C ومستخلص الزعفران عكس هذه التغييرات في الفئران .($P< 0.05$) . وتشير هذه النتائج إلى أن مستخلص الزعفران ومكوناته الفعالة قد تحمي من تلف الكبد والكلى المزمن والحاد الناجم عن مادة الأكريلاميد. علاوة على ذلك، قد تكون هذه المواد الكيميائية فعالة في مكافحة السمية.

الكلمات المفتاحية: مستخلص الزعفران، الأكريلاميد، الكبد، الكلى وفيتامين C.