Evaluation of the safety and antioxidant activities of *Crocus sativus* and *Propolis* ethanolic extracts

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**KEYWORDS**

*Crocus sativus*; Propolis; Acute toxicity; Sub-chronic toxicity; Antioxidant; Rats

**Abstract** The possible toxicological effects and *in vitro* antioxidant activity of the ethanolic extracts of *Crocus sativus* and *Propolis* were investigated. Both extracts did not cause any mortalities or signs of toxicity in mice when administered orally at doses up to 5 g/kg b.wt. In the sub-chronic study; the tested extracts did not produce any significant change in liver and kidney functions of rats, following oral administration for 8 successive weeks at doses of 500 mg/kg b.wt. of each. *Propolis* showed remarkable *in vitro* antioxidant activity at concentrations of (40–100 mg/ml). In contrast, the ethanolic extract of *C. sativus* ethanolic extract showed weak antioxidant activity in concentrations of (1–10 mg/ml) while at concentrations of (20–100 mg/ml) failed to exhibit any antioxidant activity. It was concluded that: both extracts were non-toxic, as they did not cause any mortalities or signs of toxicity in mice when administered orally at doses up to 5 g/kg b.wt. Daily oral administration of *C. sativus*, *Propolis* ethanolic extracts alone or in combination for 8 successive weeks to rats was quiet safe and didn’t cause any toxic changes in liver and kidney.

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1. Introduction

*Crocus sativus* L., commonly known as saffron, is a perennial stemless herb of the *Iridaceae* family. It is widely cultivated in Spain and Iran but also cultivated on a lower scale in other countries, such as Italy, India, France and Egypt. The name saffron comes from the Arabic za’faran, which means yellow (Rios et al., 1996). Saffron was used in folk medicine as an anodyne, antispasmodic, eupetic, gingival sedative, antac- tarrhal, nerve sedative, carminative, diaphoretic, expectorant, stomachic, aphrodisiac and emmenagogue (Rios et al., 1996). Saffron can also be used topically to help clear up sores and to reduce the discomfort of teething infants (Abdullaev and Espinosa-Aguirre, 2004; Schmidt et al., 2007). Furthermore, modern pharmacological studies have demonstrated that saffron extract or its active constituents have antioxidant activity using di-phenyl picryl hydra- zyl method (DPPH) was used to investigate their possible free radical scavenging activity.

2. Methods

2.1. Natural remedies

*C. sativus* (saffron) and *Propolis* were purchased from the local market (Agricultural Seeds, Spices and Medicinal Plants Co., Abd El-Rahman M. Harraz) in April, 2008, stored at 2–4 °C and were identified by Dr. Salwa Ali Kawashty, Prof. of Phytochemistry and Plant Systematic Department, National Research Centre (NRC), Egypt.

2.2. Preparation of ethanolic extracts

2.2.1. Preparation of ethanolic extract of *C. sativus*

One hundred g of *C. sativus* stigmas (saffron stigmas) were macerated for 3 days in one litre of 80% ethanol at room temperature. The ethanolic extract was filtered using filter paper. The filtrate was concentrated under vacuum using the rotatory evaporator (40 °C), then percolated several times till exhaustion to yield 38 g of dark red residues. The ethanolic extract was chilled in refrigerator until use (Akhondzadeh et al., 2005).

2.2.2. Preparation of ethanolic extract of *Propolis*

Dried milled, crude *Propolis* (100 g) was extracted in a dark place at 4 °C for 3 days using one litre of 80% ethanol. The extract was filtered using Büchner apparatus then concentrated under vacuum using the rotatory evaporator (40 °C) to yield 40 g of dried *Propolis* ethanolic extract. The extract was chilled in refrigerator until use (Moreno et al., 2000).

2.3. Phytochemical investigation

*C. sativus* and *Propolis* ethanolic extracts were analyzed for the presence of carbohydrates and/or glycosides using Molisch’s reagent, (Molisch, 1963). Flavonoids were detected using Neu’s reagent (Naturstoff reagent), (Neu, 1956). Sterols and/or triterpenes and volatile oils were detected according to (Liebermann and Burchard, 1890). Tannins were detected using Ferric chloride reagent, (Smith, 1960). Coumarins, Alka- loids and nitrogenous bases were detected according to the method of Stahl (1969).

2.4. Experimental animals

Mice and rats used in this investigation were obtained from The Animal House, NRC, Cairo. Mature albino mice of 20–25 g b.wt. each, of both sexes were used. Mature Sprague Dawley rats of both sexes, 150–200 g b.wt. were used. All animals were housed in hygienic cages in well ventilated rooms with exhaust fans; received standard pellet diet and water were provided *ad libitum*.

All animal procedures were performed after approval from the Ethics Committee of The National Research Centre- Egypt and in accordance with the recommendations of the proper care and use of laboratory animals.

2.5. Acute toxicity and median lethal dose (*LD*<sub>50</sub>) test

The acute oral toxicity and median lethal dose (*LD*<sub>50</sub>) of the ethanolic extracts of *C. sativus* and *Propolis* were estimated in mice (Lorke, 1983). In a pilot experiment, three groups each of five mice received the tested extracts suspended in a vehicle
(1% v/v Tween 80) at doses of 10, 100, and 1000 mg/kg b.wt., respectively. Animals were observed for 24 h for signs of toxicity and number of deaths. From the results of the preliminary test, doses of 2000, 3000, 4000 and 5000 mg/kg b.wt. of both extracts were administered to new animal groups, each of 10 mice. Control animals were received the vehicle and kept under the same conditions without any treatments. Signs of toxicity and number of deaths per dose in 24 h were recorded.

2.6. Sub-chronic toxicity

The effect of prolonged oral administration of the ethanolic extracts of C. sativus, Propolis and their combination on liver and kidney functions, body weight gain, food consumption and food conversion ratio (FCR) was evaluated in rats. Histopathological changes of liver and kidney were also assessed.

Forty rats were randomly divided into 4 equal groups. Rats of the 1st group were given the vehicle (1% v/v Tween 80) in a dose of 5 ml/kg b.wt and left as normal control. The 2nd and 3rd groups of the rats were administered the ethanolic extract of C. sativus and Propolis, respectively, in a dose of 500 mg/kg b.wt. The 4th group was medicated with a combination of both C. sativus (250 mg/kg b.wt) and Propolis (250 mg/kg b.wt) extracts. All medications were administered orally via the aid of an oral tube for 8 consecutive weeks. The animals were observed for signs of abnormalities throughout the experiment. Blood samples (2 ml) were collected from the retro-orbital venous plexus of each rat into clean centrifuge tubes at day 0, then 4 and 8 weeks post-extracts administration. Blood samples that were taken for biochemical examinations were taken without anticoagulant, from which clear sera were separate with Pasteur pipette into sterile serum sample tubes at day 0, then weekly for 8 weeks. Livers and kidneys were collected at the same period.

2.6.1. Measurement of liver and kidney function markers

Liver function was evaluated by measuring the serum activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) following the method of Reitman and Frankel (1957). Serum concentrations of creatinine and urea were determined colorimetrically as measures of kidney function according to Kroll et al. (1987) and Wills and Savory (1981), respectively.

2.6.2. Effect on body weight gain and relative organs weight

Body weight of all rats was recorded at the beginning of the study and then weekly for 8 weeks. Livers and kidneys were collected from each rat and weighed to determine the relative organ weight (ROW) as described by Chavalitthumrong et al. (2004).

\[
\text{ROW}(kg) = \frac{[\text{organ weight}(g)/\text{body weight}(g)] \times 1000}
\]

2.6.3. Effect on food consumption and food conversion ratio

A known weighed amount of food was supplied to animals of each group daily in the morning, then the remaining amount after 24 h was weighed and subtracted from the original amount of food. The average amount of food consumed per group was calculated and recorded weekly. Food conversion ratio (FCR) was calculated according to Brady (1968) using the following formula:

\[
\text{FCR} = \frac{\text{Food consumption in a given period}}{\text{body weight at the same period}}
\]

2.6.4. Histopathological examination

At the end of the experiment, animals were decapitated and tissue samples including liver and kidney were taken to investigate the histopathological changes. Tissues were then fixed in 10% buffered formalin solution (formol saline 10%). The fixed specimens were then trimmed, washed and dehydrated in ascending grades of alcohol, cleared in xylene, embedded in paraffin, sectioned at 4–6 μ thickness and stained with hematoxylin and eosin as a routine stain (Carleton, 1976). Tissue slides were examined by a pathologist.

2.7. Evaluation of the antioxidant effect (in vitro)

The activity of (1,1-Diphenyl, 2-picryl hydrazyl) DPPH radical scavenging activity was investigated according to the method of Peivu et al. (1999). The DPPH shows maximum absorbency at 517 nm, which decreases in the presence of H-donor molecules, so the test compound with antioxidant activity reduces DPPH to yellow colored product, di-phenylpicrylhydrazine, and the absorbance at 517 nm declined (Burits et al., 2001).

A methanolic solution of DPPH (2.95 ml) was added to 50 μl sample (the tested extracts were dissolved in methanol at different concentrations; 1–100 mg/ml for C. sativus and 20–100 mg/ml for Propolis) in a disposable cuvette. The absorbance was measured at 517 nm at regular intervals of 15 s for 5 min. Ascorbic acid was used as a standard (at 0.1 M concentration) as described by Govindarajan et al. (2003).

Radical scavenging activity% = \( \frac{A_e - A_t}{A_e} \times 100 \)

Where \( A_e \) and \( A_t \) are the absorbance of control (DPPH) and the test extract, respectively.

2.8. Statistical analysis

Statistical analysis of results, were done using analytical software named SPSS statistics 17.0, Release (Aug. 23, 2008), Chicago, USA. Values were expressed as means ± S.E. Quantitative differences between values were statistically analyzed by least significant difference test (LSD) followed by Dunnett’s multiple comparisons test. \( P \) values <0.05 were considered to be significant.

3. Results

3.1. Phytochemical investigation

Phytochemical analysis of C. sativus and Propolis ethanolic extracts has shown that both extracts contain flavonoids, carbohydrates &/or glycosides, sterols and/or terpenes. They do not contain volatiles, coumarins, alkaloids &/or nitrogenous compounds, tannins or saponins.
3.2. Acute toxicity and median lethal dose (LD$_{50}$) test

The results revealed that all the examined doses of _C. sativus_ and _Propolis_ (up to 5000 mg/kg b.wt.) did not produce any demonstrable acute toxic effects or deaths in all groups of mice.

3.3. Sub-chronic toxicity in rats

The effect of prolonged oral administration of the tested extracts (8 successive weeks) on serum transaminases activity, serum creatinine and urea was recorded in rats (Tables 1 and 2). Oral administration of the ethanolic extract of _C. sativus_ and _Propolis_ in a dose of 500 mg/kg b.wt. and their combination in their half dose levels for 8 weeks did not affect the serum activity of AST and ALT as compared to those of the normal control rats or their basal values. The obtained results showed no significant effect on serum levels of creatinine and urea in all groups when compared to control group and when compared to their basal values.

The effect of oral administration of the ethanolic extracts of _C. sativus_, _Propolis_ and their combination for 8 successive weeks on body weight gain and relative organs weight of rats was determined (Table 3).

Ethanolic extracts of _C. sativus_, _Propolis_ and their combination showed no significant effect on body weight gain of rats all over the experimental period compared to the control group. They significantly increased the relative weights of kidneys. The relative weights of liver were significantly increased in rats that were medicated with either _C. sativus_ alone or the combination of _C. sativus_ and _Propolis_. _Propolis_ alone did not alter the relative weight of liver to any significant extent at the different times of measurement.

Daily oral administration of ethanolic extracts of _C. sativus_, _Propolis_ or their combination for 8 consecutive weeks to rats showed insignificant effect on food consumption and food

<table>
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<tr>
<th>Table 1</th>
<th>Effect of prolonged oral administration of ethanolic extracts of <em>Crocus sativus</em> (CS); <em>Propolis</em> (PP) and their combination (CS + PP) for 8 successive weeks; on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels of rats.</th>
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<td>Groups</td>
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Values represent the mean ± S.E. (n = 10).
No significant difference from control (LSD).
No significant difference from basal value of each group (Paired t-test).

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Values represent the mean ± S.E. (n = 10).

$^a$ $P < 0.05$: Statistically significant from control (LSD followed by Dunnett’s test).
conversion ratio along the experimental period when compared to control (Figs. 1–3).

3.4. Evaluation of antioxidant activity (in vitro)

The antioxidant activity of the ethanolic extract of *C. sativus*, *Propolis* and their combination (CS + PP) for 8 successive weeks showed no significant changes in the activity of serum transaminases, creatinine and blood urea nitrogen levels in all medicated groups, compared to the control. These data were supported by the absence of any abnormal histopathological findings.

In addition, the body weight gain throughout the experimental period showed insignificant difference in all extracts groups and their combination when compared to the control one. Our results are not in agreement with those obtained by Mohajeri et al. (2007). They reported that intraperitoneal administration of ethanolic extract of saffron to rats in doses of 0.35, 0.70 and 1.05 g/kg b.wt. showed no significant changes in serum urea or creatinine levels following administration of saffron stigmas tablets for 7 days in healthy volunteers.

Results of the present study are not in accordance with the findings of Newairy et al. (2009). They reported that oral administration of *Propolis* for 70 days decreased the activities of serum transaminases, creatinine and blood urea nitrogen levels in rats compared to the control. Our results are not in agreement with those obtained by Mohajeri et al. (2007). They reported that intraperitoneal administration of ethanolic extract of saffron to rats in doses of 0.35, 0.70 and 1.05 g/kg b.wt. for 2 weeks, significantly increased serum ALT, AST, urea and creatinine levels. They also reported significant decrease in the body weight gain in a dose-dependent manner. Moreover, Modaghegh et al. (2008) reported that no significant changes in serum urea or creatinine levels following administration of saffron stigmas tablets for 7 days in healthy volunteers.

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4. Discussion

The acute toxicological evaluation revealed that oral administration of the ethanolic extract of both *C. sativus* and *Propolis* in doses up to 5000 mg/kg b.wt. did not produce any demonstrable acute toxic effect or death in all the groups of mice. Accordingly, it suggested that oral LD₅₀ of the extract was higher than 5000 mg/kg b.wt. Therefore, the tested extracts can be categorized as highly safe since substances possessing LD₅₀ higher than 50 mg/kg b.wt. are non toxic (Buck et al., 1976). According to guidelines of the Organization for Economic Cooperation and Development (OECD, 2001); substances possessing LD₅₀ dose of 2000 mg/kg b.wt. or higher are categorized as unclassified and hence our extracts are found to be non-toxic.

Concerning the acute toxicity and lethality study of *C. sativus* ethanolic extract our result is in agreement with Abdullaev et al. (2003). They found that oral administration of saffron extract at concentrations from 0.1 to 5 g/kg b.wt. was non-toxic in mice. Moreover, Khare (2007) set the recommended dose of saffron stigma and styles in human as 0.5–1.5 g/day, as the dose at 1–5 g is toxic. On the other hand, the present results of acute toxicity of *Propolis* are in agreement with Arvouet-Grand et al. (1993). They reported that oral LD₅₀ of *Propolis* extract in mice was greater than 7.34 g/kg b.wt. in addition; Mohammadzadeh et al. (2007) showed that oral administration of hydroalcoholic solution of *Propolis* extract in rats at doses of (4.5, 9, 13 and 20 g/kg b.wt) has no toxic effects.
of AST and ALT in plasma but did not cause any significant change in urea and creatinine levels. Also, Sforcin et al. (2002) reported that treatment of rats with Propolis does not induce any alteration in AST level. Moreover, Mani et al., (2006) found no alteration in AST value in the serum of Propolis treated rats for (30 or 90 or 150 days) at doses of (1, 3 and 6 mg/kg/day). There was significant increase in the relative weights of liver, in the C. sativus group and the combination group. Also there was significant increase in the relative weights of kidneys in all groups when compared to that of control group. Mohammadzadeh et al. (2007) recorded slight significant increase in liver weight as a ratio of body weight in rats.

Figure 3  Histopathological examination of (a) liver and (b) kidney, (Hx.&E. X 200): (a-1) Photomicrograph of a section of liver tissue from a control rat showing normal structure. (a-2) Administration of Crocus sativus; showed mild dilatation and congestion of blood sinusoids (arrow). The central vein as well as hepatocytes appear normal in size and shape. (a-3) Administration of Propolis; showed noticeable dilatation of blood sinusoids (arrow head) denoting edema, together with cellular infiltrate around the central vein (arrow). The central vein itself shows no dilatation. (a-4) Administration of Crocus sativus and Propolis ethanolic extracts; revealed observable dilatation and congestion of blood sinusoids (arrow head). Also congestion of central vein is seen with mild cellular infiltrate around (arrow). (b-1) Photomicrograph of a section of renal tissue of a control rat showing showing normal structure. (b-2) Administration of Crocus sativus; showed normal tissue architecture, but with little widening in some tubules lumen. (b-3) Administration of Propolis; showed widening in the urinary space of the Bowman’s capsule (arrow) and in the interstitial tissue between the tubules (arrow head). (b-4) Administration of Crocus sativus and Propolis ethanolic extracts; revealed noticeable widening in the interstitial tissue in between the tubules (arrow head).
receiving Propolis hydroalcoholic solution containing 2 g/kg/day; for 9 successive weeks. Those findings were not in accordance to our results, which may be due to the difference in dose level used in their study and ours. In addition, no significant difference was observed in the amount of feed consumed weekly in Propolis-treated rats when compared to control.
Our results revealed that the ethanolic extracts of both C. sativus and Propolis either alone or in combination induced insignificant effect of on the food conversion ratio (FCR) when compared to control group. On the other hand, the histopathological examination of liver and kidney sections showed normal findings. These results are not in agreement with that obtained by Mohajeri et al. (2007) who reported that there were prominent hepatic and renal tissue injuries in saffron extract treated rats in doses up to 5 g/kg b.wt. intraperitoneally for 2 weeks. The difference between results may be attributed to the difference in dose and route of administration used. While our results are in agreement with those cited by Burdock (1998), no histological changes were observed when alcoholic extract of Propolis was administered in drinking water to rats in a 30-days study.

The variability in results from study to study was discussed by Raina et al. (1996) and Maggi et al. (2009) whose assured that the harvest time, processing temperature, storage and packaging of saffron, highly affects the quality of the final product. As during the drying process of saffron stigmas, significant modifications are observed in the color, taste and aroma. Since, different drying processes depending on the country of production result in different characteristics and qualities of saffron. Also Fogden and Neuberger (2003) cited that the active constituents themselves are influenced by a wide range of factors: harvest season, preparation methods, plant species, and location including altitude and climate, and quality control. Other concerns include the misidentification of herbs in a product either accidentally or deliberately, varying quality of herbs and contamination of products by heavy metals, chemicals (e.g. pesticides) or drugs (e.g. digitalis or corticosteroids).

Free radical-scavenging activity of both C. sativus and Propolis ethanolic extracts were evaluated, using a method based on the reduction of methanolic solution of DPPH (di-phenyl picryl hydrazil). C. sativus ethanolic extract in concentrations of (20, 40, 60, 80, and 100 mg/ml), showed no antioxidant activity compared to ascorbic acid. While in concentrations of (1, 2, 4, 6, 8, and 10 mg/ml) showed weak antioxidant activity. In this respect Assimopoulou et al. (2005) and Chen et al. (2008) found that methanolic and ethanolic saffron extracts exhibited appreciable scavenging properties against DPPH radicals, which were concentration dependant. They referred the significant antioxidant activity of the saffron extract to the synergistic action of its bioactive constituents, crocin and safranal. In addition to that Kanakis et al. (2009) tested the antioxidant activity of some saffron derivatives as safranal, crocetin, dimethylcrocein using the DPPH antioxidant activity assay. The achieved results demonstrated that the free radical scavenging activity of crocetin was higher than that of dimethylcrocein and by increasing their concentrations, a decrease in the antioxidant activity was observed. They explained this finding by the fact that higher concentrations of dimethylcrocein or crocins show pro-oxidant effect since theoretically it could generate more radicals than it consumes.

In the present study, the ethanolic extract of Propolis exhibited a remarkable in vitro antioxidant activity at the different concentrations used. This finding is in agreement with Banskota et al. (2000) and Moreno et al. (2000) who reported that water and alcoholic Propolis extracts have scavenging activity towards DPPH free radical in a similar extent. This antioxidant activity was attributed to the flavonoid content of Propolis (Isla et al., 2001; Gardana et al., 2007; Xu et al., 2009). The DPPH test provides information on the reactivity of drugs with a stable free radical, but this test does not provide a clear-cut definition of antioxidant effect (Tseng et al., 1995). Therefore, further in vivo tests are required to investigate the possible antioxidant, hepatoprotective and/or hepatocurative effects of both C. sativus and Propolis ethanolic extracts.

5. Conclusion

Ethanolic extracts of both C. sativus and Propolis were harmless, as they did not cause any mortalities or signs of toxicity in mice when administered orally at doses up to 5 g/kg b.wt. Daily oral administration of C. sativus, Propolis ethanolic extracts and their combination for 8 successive weeks in rats was quiet safe and didn’t cause any toxic changes in liver and kidney. Also no changes were recorded in body weight gain, food consumption and food conversion rate when compared to normal rats. Propolis showed remarkable in vitro antioxidant activity more than C. sativus at the concentrations under investigation.

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References

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