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The effects of Crocin from red saffron flower on the innate and humoral immune systems of domestic short hair cats

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Abstract

Crocin, the primary active component of the red saffron flower (*Crocus sativus*), possesses a variety of biological and antioxidant properties. This study aimed to evaluate its effects on the immune system of domestic short hair (DSH) cats compared to the immunosuppressive drug cyclosporine. A total of 32 cats were divided into four groups: G1) received crocin at a dosage of 10 mg/kg body weight, G2) received cyclosporine at 7 mg/kg body weight for two weeks, followed by crocin for an additional two weeks, G3) received only cyclosporine for 30 days, and G4) served as the control group. Blood samples were collected every ten days to monitor changes in immune parameters. Statistical analysis revealed significant differences ($p<0.05$) in the concentrations of immunoglobulin A (IgA), IgG, IgM, and neutrophil counts among the treatment and control groups. However, there were no significant changes observed in lymphocyte and monocyte counts, or the percentage of phagocytes. In the group receiving crocin, a significant increase in immunoglobulin M was observed between days 0 to 10, and from days 20 to 30, indicating a continued enhancement of the immune response. Immunoglobulin G levels remained stable until day 20, after which a significant increasing trend was observed, alongside notable differences between the groups throughout the study period. Furthermore, immunoglobulin M levels in all groups showed significant changes with the saffron group starting from day 20 onward, indicating a consistent upward trend. In conclusion, the findings suggest that the incorporation of saffron significantly enhances the humoral immune response in cats, specifically through increased levels of immunoglobulin A, G, and M. However, saffron did not demonstrate a notable effect on the innate immune system, as indicated by unchanged lymphocyte and monocyte counts. Based on these results, the use of saffron in veterinary medicine and the food industry is recommended for its potential immunomodulatory effects.

1. Introduction

Herbal medicines have long been popular in human and veterinary medicine due to their indigenous nature and good healing effects dating back to centuries ago. Since the beginning of the 21st century, novel therapeutic compounds with outstanding healing effects have been extracted from medicinal plants and used around the world (Shahrajabian and Sun 2023). Saffron plant (*Crocus sativus* L.) of the Iridaceae family is a small, bulbous and perennial plant with 10-30 cm height, whose bulb is almost spherical and covered with thin brown membranes (Cardone et al. 2020). The flowers are very beautiful and have 6 purple or pink petals. They possess three stamens and a pistil leading to a three-branched stigma with red to orange color. It is the stigma of three branches that is used as saffron, a well-known aromatic spice in foods (Kothari et al. 2021). Typically, saffron is a tropical plant native to the southwest Asia, growing better in moderate and hot climates with dry summer and mild autumn. The plant is active during November until April, while it turns back into a latent phase until months later (Shokrpour 2019). Beyond using as a popular spice, saffron has been used to cure a wide variety of diseases, including cardiovascular disorders (Ghaffari and Roshanravan 2019), autoimmunity disorders (Poursamimi et al. 2020), inflammatory bowel disease (Khorasany and Hosseinzadeh 2016), hepatitis (Karimi et al. 2021), nephritis (Zarei and Elyasi 2022), and cognitive dysfunctions (Rajabian et al. 2019). The crocetin is the primary stigma component in saffron, forming several glucosidic components, including crocin, picrocrocin and safranal (Giaccio 2004). Picrocrocin, a monoterpene glycoside, is safranal precursor that is commonly present in saffron and responsible for its bitter taste. Also, safranal makes up about 70-60% of the volatile part of saffron and is the cause of the saffron aroma. Crocin is a water-soluble carotenoid, yielding the color of saffron, with biologically-diverse advantageous properties (Omidkhoda and Hosseinzadeh 2022).

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The immune system consists of humoral and cell-mediated immune cells and associated molecules, and functions as a biological machinery to protect the body against pathogenic agents and their associated substances that can cause a range of diseases (Nicholson 2016). It has long been recognized that an imbalanced immune response may be a contributing factor in the development of various disorders, which may result from the exposure to extreme temperatures and sunlight, pathogenic agents, corrosive chemicals, and physical injury (Giardino et al. 2016). Inflammation-driven oxidative stress may be a potent cause for multiple diseases, which occur through the induction of inflammatory markers such as tumor necrosis factor alpha (TNF-α), tissue growth factor beta (TGF-β), interleukin 1b (IL-1b), IL-6, and IL-8 (Chatterjee 2016). Cyclosporine is an immunosuppressant being used in human and veterinary medicine. However, it has been shown to be associated with acute and chronic nephrotoxicity, neurotoxicity, hyperlipidemia, hyperkalemia, and thrombotic microangiopathy (Patocka et al. 2021). Many researchers are currently investigating to discover natural, herb-based therapeutic substances for the prevention and treatment of inflammatory and immune-related diseases. In the present study, the immunomodulatory effects of crocin derived from red saffron flower was evaluated on immunological parameters in DSH cats.

Recent research has shown that saffron and its active compound crocin have significant immunomodulatory properties. In animal models, crocin has been found to enhance both humoral and cellular immunity by boosting the production of immunoglobulins and modulating immune cell function (Tehran et al. 2024; Vijayabhargava and Asad 2011). On the other hand, cyclosporine, a widely used immunosuppressive drug in veterinary medicine, suppresses cellular immunity by inhibiting T-cell activation. While effective in treating autoimmune diseases and preventing organ rejection, cyclosporine is associated with several adverse effects, including nephrotoxicity and hepatotoxicity (Patocka et al. 2021). This contrast between saffron's immune-enhancing effects and cyclosporine's immunosuppressive action highlights the importance of investigating natural alternatives like crocin to mitigate immune-related diseases with fewer side effects.

2. Materials and Methods

2.1. Animals and groups

In this study, 32 domestic short hair (DSH) male cats weighing 2-3 kg were used and kept in separate cages under standard temperature (25-30°C), 12-hour light-dark cycle, and constant access to food and water. A uniform diet was provided to the cats and they were examined two weeks before the start of the experiment to ensure that they were healthy. Next, all cats underwent a continuous antiparasitic therapy regimen consisting of praziquantel administered daily for five days, followed by mebendazole on day 6. Additionally, ivermectin was injected subcutaneously on two occasions to eliminate cutaneous parasites. The cats were randomly divided into four groups with eight in each, as follows: G1) cats received crocin (10 mg/kg) of red saffron along with regular food and water for 4 weeks, G2) cats received cyclosporine (7 mg/kg) for only 2 weeks, G3) cats received cyclosporine (7 mg/kg) for 2 weeks, then the drug was excluded and the animals received crocin (10 mg/kg) of red saffron for 2 weeks, and G4) control group received only regular food and water. This study was conducted in the Veterinary Hospital of Islamic Azad University, Shahrekord branch, western Iran. During the experiment, the cats were fed with dry food and their vital signs such as heart rate, breathing rate, and temperature were recorded daily. Crocin (Krocina) and cyclosporine (Neoral®) were fed daily through commercially-available pills. The maintenance area of cats was cleaned every day and the floors of the cages were disinfected once a week.

2.2. Blood collection

Cephalic vein blood collection was done in the examined cats. Cats were initially restrained, the area was shaved and disinfected by 70% alcohol, then blood was taken slowly in 5 ml syringes. Blood sampling was done four times during the investigation on days zero, 10, 20, and 30. Subsequently, the collected blood specimens were transferred into two specific tubes, one containing an anticoagulant EDTA and the second without anticoagulant. The blood samples were immediately transferred to the laboratory of Shahrekord Azad University.

2.3. Blood cells enumeration

Blood cell parameters including red blood cell (RBC) and white blood cell (WBC) counts, hemoglobin (Hb), and hematocrit (Hct) were evaluated in blood specimens containing EDTA, using an automatic cell counter device. Moreover, the enumeration of lymphocytes, monocytes, neutrophils, eosinophils, as well as phagocytes was done by light microscopy of the Giemsa-stained thin blood smears.

2.4. Humoral immune response and phagocytosis analysis

Evaluation of the antibodies (IgA, IgG, and IgM) was done in cat sera using commercial spectrophotometric kits (Roche, Germany) using Cobas Integra 400 Plus Chemistry Analyzer (Roche, Germany). For phagocytosis analysis, 5 ml of Staphylococcus bacteria juice was added to 1 ml of fresh blood and incubated overnight at 35 °C. Then the homogenized sample was used for slide preparation followed by Giemsa staining. In the prepared smear, 100 neutrophils were counted (100× magnification) and reported as the number of cells that had phagocytosed bacteria as a factor percentage.

2.5. Statistical analysis

Statistical analysis was performed using SPSS v26 software. Descriptive data were described as mean ± standard error. After normal data distribution, one-way ANOVA and post hoc LSD test were used for analysis of blood sampling between the four groups. To investigate the trend of changes among four groups at 4 different blood sampling times (days zero, 10, 20, and 30) repeated measures data analysis test was performed. The significant level was set as $p \leq 0.05$.

3. Results

In the study of mean IgA (mg/dL) levels in DSH cats (Table 1), G1 exhibited the highest level of 52.75 mg/dL by Day 30, demonstrating a significant immunomodulatory effect of crocin. Statistical analysis revealed significant differences among the groups on Day 10, 20, and 30 ($p < 0.001$), particularly between G1 and the other groups (G2, G3, and G4), indicating that crocin treatment markedly enhanced IgA levels. In contrast, G2 and G3 showed lower IgA levels, with G2 peaking at 16.75 mg/dL on Day 0 and decreasing to 15.25 mg/dL by Day 30, while the control group, G4, maintained stable levels with a peak of 17.75 mg/dL on Day 20 (Table 1). The analysis of mean IgG (mg/dL) levels in DSH cats (Table 2) showed that G1 exhibited significantly higher levels, peaking at 384 mg/dL on Day 20, indicating the strong immunomodulatory effect of crocin. Significant differences were observed among the groups on Days 10 ($p = 0.003$), 20 ($p < 0.001$), and 30 ($p < 0.001$). Pairwise comparisons revealed significant differences between G1 and G2 ($p < 0.001$), G1 and G3 ($p = 0.001$), and G1 and G4 ($p = 0.005$) on Day 10. On Day 30, differences remained significant between G1 and G2 and G4 ($p < 0.001$), as well as between G1 and G3 ($p = 0.04$). In contrast, G2, G3, and G4 maintained lower IgG levels, underscoring crocin's effectiveness.

Table 1 Serum IgA (mg/dL) levels of DSH cats among experimental groups and blood collection periods

Groups	Day 0	Day 10	Day 20	Day 30
G1	40.25±7.43	43.75±7.46	50.50±8.42	52.75±8.43
G2	16.75±1.10	11.50±1.32	13.40±1.52	15.25±1.25
G3	14.50±1.19	10.50±1.25	11.75±1.49	13.75±1.70
G4	15.75±0.47	17.50±0.86	17.75±1.31	16.50±1.65

G1) cats received crocin (10 mg/kg) of red saffron along with regular food and wa
G2) cats received cyclosporine (7 mg/kg) for only 2 weeks
G3) cats received cyclosporine (7 mg/kg) for 2 weeks, then the drug was excluded
G4) control group received only regular food and water

Table 2 Serum IgG (mg/dL) levels of DSH cats among experimental groups and blood collection periods

Groups	Day 0	Day 10	Day 20	Day 30
G1	196±35.08	316.5±52.18	384±1.63	325.8±18.86
G2	189.8±26.25	150.5±6.29	154.5±5.61	161.5±6.5
G3	174±9.08	138±17.75	285±5.19	276±21.42
G4	179.3±8.09	180±6.68	178±9.68	176.3±18.94

G1) cats received crocin (10 mg/kg) of red saffron along with regular food and wa
G2) cats received cyclosporine (7 mg/kg) for only 2 weeks
G3) cats received cyclosporine (7 mg/kg) for 2 weeks, then the drug was excluded
G4) control group received only regular food and water

The analysis of IgM levels in DSH cats (Table 3) indicated that G1 showed a significant increase, reaching 60.0 mg/dL by Day 30. Statistical evaluations revealed significant differences among groups on Day 20 ($p = 0.002$), with significant pairwise differences between G1 and G2 ($p = 0.022$). Additionally, on Day 30, significant differences were noted between G1 and G2 ($p = 0.025$) and G1 and G4 ($p = 0.021$). In contrast, no significant differences were found between G1 and G3 on both Day 20 ($p = 0.086$) and Day 30 ($p = 0.062$).

Table 3 Serum IgM (mg/dL) levels of DSH cats among experimental groups and blood collection periods

Groups	Day 0	Day 10	Day 20	Day 30
G1	47.00±7.11	50.50±6.94	56.00±5.88	60.00±6.97
G2	84.75±9.32	60.00±8.52	77.00±6.60	80.50±5.43
G3	43.25±4.32	39.50±4.34	41.00±3.71	43.50±4.40
G4	39.00±6.54	40.50±6.34	41.25±6.01	38.75±5.58

G1) cats received crocin (10 mg/kg) of red saffron along with regular food and wa
G2) cats received cyclosporine (7 mg/kg) for only 2 weeks
G3) cats received cyclosporine (7 mg/kg) for 2 weeks, then the drug was excluded
G4) control group received only regular food and water

Regarding neutrophil counts (Table 4), a significant difference was observed among groups on Day 10 ($p = 0.035$), but no significant differences were detected on Days 20 ($p = 0.639$) and 30 ($p = 0.597$). Similarly, lymphocyte counts (Table 5) exhibited no significant differences on Day 10 ($p = 0.317$), indicating consistent levels across groups. Lastly, phagocytosis percentages (Table 6) also showed no significant differences on Day 10 ($p = 0.317$), reflecting a stable immune response across the experimental groups.

Table 4 Neutrophil count (cells/µL x 10^3) in DSH cats among experimental groups and blood collection periods

Groups	Day 0	Day 10	Day 20	Day 30
G1	71.90±2.02	60.67±3.59	65.47±4.41	70.05±3.76
G2	65.32±2.00	68.07±2.36	69.70±1.94	65.07±2.65
G3	68.07±1.76	55.35±1.19	64.55±1.61	68.60±0.91
G4	68.75±3.85	65.90±3.56	68.20±3.64	68.37±2.24

G1) cats received crocin (10 mg/kg) of red saffron along with regular food and wa
G2) cats received cyclosporine (7 mg/kg) for only 2 weeks
G3) cats received cyclosporine (7 mg/kg) for 2 weeks, then the drug was excluded
G4) control group received only regular food and water

4. Discussion

The immune system is constantly exposed to pathogenic and opportunistic microorganisms. To combat such invasions, it relies on the innate and adaptive immune responses (Nicholson 2016). The immunomodulatory properties of medicinal herbs have long been documented, with saffron, native to Iran, being

Table 5 Lymphocyte count (cells/μL x 10³) in DSH cats among experimental groups and blood collection periods

Groups	Day 0	Day 10	Day 20	Day 30
G1	26.00±1.73	25.75±1.93	25.25±3.30	24.50±2.72
G2	32.00±2.04	27.50±2.10	28.50±2.06	30.75±2.46
G3	30.25±1.79	31.50±1.32	28.75±3.19	26.50±1.19
G4	28.37±3.85	29.25±2.92	28.25±3.25	28.00±2.61

G1) cats received crocin (10 mg/kg) of red saffron along with regular food and wa
G2) cats received cyclosporine (7 mg/kg) for only 2 weeks
G3) cats received cyclosporine (7 mg/kg) for 2 weeks, then the drug was excluded
G4) control group received only regular food and water

particularly recognized for its therapeutic potential (Kothari et al. 2021). This study aimed to assess the immunological effects of crocin, an active compound derived from saffron, on immune parameters in domestic short hair (DSH) cats. In this study, the cats treated with crocin (G1) exhibited significant increases in IgA and IgG levels compared to the control and other groups, with these effects becoming particularly evident after day 20. The rise in IgA levels in G1 contrasted with the lower, stable IgA levels seen in the other groups. Similarly, IgG levels in G1 peaked on day 20 and remained elevated, demonstrating crocin's strong immunomodulatory effect. These differences were statistically significant across multiple time points, particularly when comparing G1 to G2, G3, and G4. Although IgM levels did not differ significantly between G1 and the other groups, a marked increase in IgM was observed within G1 from day 20 to day 30, suggesting crocin's continued influence on humoral immunity. Neutrophil counts showed an initial rise across all groups, which could be linked to immune system stimulation and crocin's antioxidant properties. However, neutrophil levels gradually decreased as the study progressed, though these changes were not statistically significant. This trend may indicate a transient inflammatory response, with neutrophils returning to baseline levels after initial stimulation. No significant changes were found in lymphocyte and monocyte counts or phagocytosis percentages across the groups, suggesting that crocin did not have a substantial impact on these aspects of innate immunity in this study.

Table 6 Phagocytosis percentage in DSH cats among experimental groups and blood collection periods

Groups	Day 0	Day 10	Day 20	Day 30
G1	26.00±1.73	25.75±1.93	25.25±3.30	24.50±2.72
G2	32.00±2.04	27.50±2.10	28.50±2.06	30.75±2.46
G3	30.25±1.79	31.50±1.32	28.75±3.19	26.50±1.19
G4	28.37±3.85	29.25±2.92	28.25±3.25	28.00±2.61

G1) cats received crocin (10 mg/kg) of red saffron along with regular food and wa
G2) cats received cyclosporine (7 mg/kg) for only 2 weeks
G3) cats received cyclosporine (7 mg/kg) for 2 weeks, then the drug was excluded
G4) control group received only regular food and water

The findings on IgG levels in this study were consistent with those reported by (Kianbakht et al. 2003), who found that saffron boosted humoral immunity in humans, including increased IgG levels over time. However, differences in monocyte responses between species may explain the discrepancies in the findings of this study. Babaei et al. (2014) also noted increased IgG levels in mice following saffron administration, further supporting crocin's immunomodulatory effects. Similarly, Kianbakht and Ghazavi (2011) demonstrated that saffron influenced immune parameters, including a temporary increase in monocytes and IgG, followed by a return to baseline levels over time. These results align with the findings of this study regarding IgG, though differences in monocyte and IgM responses may reflect species-specific effects or variations in treatment duration.

Research from Qazvin (Kianbakht 2008) and Mashhad (Zeinali et al. 2019) also highlighted the immune-boosting properties of saffron and its components, emphasizing their potential in treating immune-related diseases. While our study observed significant effects on humoral immunity, differences in innate immune responses might be due to the specific doses, species, and experimental timelines used. Hosseini et al. (2018) demonstrated that crocin is rapidly transformed into crocetin and distributed throughout various tissues, suggesting its wide-reaching physiological effects. Our findings indicate that crocin significantly modulates humoral immunity in DSH cats, though its impact on the innate immune system appears limited (Hosseini et al. 2018).

In a Chinese study, crocin was found to reduce inflammation and inhibit key inflammatory mediators, such as TNF-α and IL-6, in rats (Liu et al. 2018). In contrast, our study found no significant inflammatory effects in G1, though the initial increase in neutrophils might suggest a brief inflammatory response that resolved over time ($p > 0.05$). While antioxidant properties of saffron were not the primary focus of this paper, other studies have highlighted their importance in reducing oxidative stress and preventing various diseases (Creda-Bernard et al. 2022). Based on Avicenna's teachings and modern research, saffron's active components, particularly crocin, are known to neutralize reactive oxygen species (ROS) and alleviate inflammation (Hashemzaei et al. 2020). Although no significant reduction in monocytes was observed in our study, this aligns with reports of saffron's immune-modulating effects, particularly in humoral immunity.

5. Conclusions

In the present study, immunomodulatory effects of crocin from red saffron was substantiated in DSH cats. It is further suggested to evaluate the biological effects of this valuable herbal-based substance on immunodeficiency and immuno-suppressive diseases. Moreover, the administration route of crocin need to be further investigated and standardised.

Declarations

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Conflict of interest: The authors declare that they have no conflicts of interest related to this study

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