Acta fytotechn zootechn, 28, 2025(1): 14–20
http://www.acta.fapz.uniag.sk

Original Paper

Investigation of the Clinical Efficacy of Quercetin in Feline Atopic Dermatitis Syndrome

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Article Details: Received: 2025-01-13 | Accepted: 2025-01-24 | Available online: 2025-03-31

https://doi.org/10.15414/afz.2025.28.01.14-20

Feline Atopic Skin Syndrome (FASS) is a common dermatological condition in cats, linked to oxidative stress and variable skin lesions. While glucocorticoids and antihistamines are standard treatments, the inconsistent feasibility of allergen avoidance and immunotherapies necessitates the use of anti-inflammatory and immunosuppressive agents like prednisolone or cyclosporine. However, their side effects can limit long-term use, driving research into alternative therapies to mitigate these drawbacks.This study aimed to evaluate the effects of quercetin on oxidative stress parameters and clinical findings in cats with FASS. Thirty-six cats were included in the study and divided into two groups: cats diagnosed with FASS (n = 27) and healthy cats (n = 9). Additionally, cats diagnosed with FASS were grouped according to their clinical presentations, which included Head-and-Neck Pruritus (HNP), Self-Induced Alopecia (SIA), Miliary Dermatitis (MD), Eosinophilic Granuloma Complex (EGC), and Dermatitis. Quercetin treatment (3 mg.kg^{-1}) was administered orally for 14 days in both groups. Clinical findings were assessed on days 0, 7, and 14 using SCORFAD, FEDESI, and VAS scoring systems, alongside blood analyses for thiol-disulfide balance. Significant reductions in clinical scores (FEDESI, SCORFAD, VAS) were observed in the HNP and MD groups, while improvement was limited to one cat in the SIA group. Although no significant differences in thiol-disulfide balance were detected between groups, slight reductions in total thiol and disulfide levels were noted. These results indicate that quercetin may alleviate oxidative stress and improve clinical outcomes in FASS treatment.

Keywords: atopy, cat, quercetin

1 Introduction

Feline Atopic Skin Syndrome (FASS) is defined as a pruritic and inflammatory skin condition triggered by environmental allergens and is commonly encountered in cats (Halliwell et al., 2021). FASS encompasses a broad range of hypersensitivity-related disorders, including allergic dermatitis, asthma, respiratory diseases, and gastrointestinal disturbances associated with environmental allergens and food sensitivities. Unlike dogs, cats exhibit a pleomorphic clinical response to these allergens, and there is ongoing debate regarding the role of IgE in this process. Consequently, varying terminologies have been proposed for feline environmental allergen sensitivity, with the most recent term being "Feline Atopic Skin Syndrome (FASS)" (Hobi et al., 2011; Santoro et al., 2021).

FASS manifests in diverse skin lesions in cats, characterized by clinical presentations such as miliary dermatitis (MD), self-induced alopecia (SIA), head and neck pruritus (HNP), and eosinophilic granuloma complex (EGC) (Hobi et al., 2011). MD presents as pruritic and crusted papules, while SIA leads to excessive hair loss and vomiting in affected cats (Scott and Miller, 2013). HNP results in severe pruritus localized to the head and neck, and EGC is marked by painless lesions, such as indolent ulcers and granulomas (Ravens et al., 2014). Among FASS-affected cats, the most frequently observed reactions are SIA (60.1%) and HNP (43.0%), with these reactions often concentrated around the ears, head, and neck (Hobi et al., 2011).

Glucocorticoids and antihistamines are commonly employed in the treatment of FASS. However, due to the inability to prevent allergen exposure or implement specific immunotherapies, anti-inflammatory and

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immunosuppressive drugs, such as prednisolone or cyclosporine, are often required (Olivry and Saridomichelakis, 2013). The side effects of these drugs, however, limit their usage in some cases, highlighting the need for alternative therapies with fewer adverse effects. Quercetin, with its anti-inflammatory and antioxidant properties, has emerged as a potential therapeutic agent for managing these inflammatory processes (Ganz et al., 2012; Mueller et al., 2021). Although studies on Quercetin's effects in domestic animals, including cats, are limited, it demonstrates efficacy in skin conditions such as atopic dermatitis (AD) by reducing the production of reactive oxygen species, inhibiting oxidative stress-induced cell death in keratinocytes, and modulating inflammatory signaling pathways (Yang et al., 2014; Potenza et al., 2008). Moreover, quercetin inhibits apoptosis by suppressing caspase-8 and mitochondrial pathways, reduces inflammation by modulating NF-κB and AP-1 signaling, and protects against oxidative stress via the activation of the Nrf2 pathway (Kim et al., 2013; Karuppagounder et al., 2015). In a mouse model of house dust mite-induced AD, quercetin demonstrated reduced inflammation and oxidative stress. Additionally, quercetin effectively suppressed UV-B-induced skin erythema in patients with nickel-patch contact dermatitis (Weng et al., 2012). In sarcoidosis patients, quercetin significantly reduced inflammatory markers such as TNF-α and IL-8 (Pfeuffer et al., 2013). Conversely, a study by Furst and Zundorf (2014) found no effect of quercetin on inflammatory responses in healthy individuals. In osteoarthritis patients, a combination of glucosamine, chondroitin, and quercetin alleviated symptoms (Kanzaki et al., 2012). However, quercetin's limited bioavailability underscores the need for new formulations to enhance its therapeutic efficacy (Weng et al., 2012).

This study aimed to evaluate the clinical efficacy and effects of quercetin on oxidative balance in cats with FASS.

2 Material and Methods

2.1 Animal Material and Group Design

The study was conducted on cats admitted to the Department of Internal Medicine, Faculty of Veterinary Medicine, Aydın Adnan Menderes University. Cats aged 12 months and older of both sexes (sterilized and unsterilized) were included in the study. The animals were divided into two groups: diseased cats (n = 27) and healthy controls (n = 9). Healthy cats, consisting of mixed breeds from both genders, were selected to match the diseased group in terms of age, breed, and gender. The health status of the control group was confirmed based on anamnesis, clinical evaluation, and laboratory tests. Cats in the diseased group were diagnosed with Feline Atopic Skin Syndrome (FASS) and underwent dermatological examination (Santoro et al., 2021).

2.2 Clinical Evaluation and Scoring

Cats diagnosed with FASS were initially assessed as a single group before being further categorized into subgroups based on their specific clinical presentations. The diagnosis of FASS was established based on the presence of pruritus and characteristic lesion patterns, including head and neck excoriations, eosinophilic dermatitis, self-induced alopecia, and/or miliary dermatitis. The determination of subgroups involved diagnostic techniques such as skin scrapings, biopsy, Wood's lamp examination, trichogram analysis, and bacterial or fungal cultures. Allergic food reactions were excluded using elimination diets with commercial hydrolyzed formulas. Cats with a history of topical glucocorticoid or oral glucocorticoid treatment within the previous two weeks, injectable glucocorticoid treatment within eight weeks, or cyclosporine or oclacitinib therapy within four weeks, as well as those with concurrent diseases or positive FIV/FeLV serological tests, were excluded from the study.

Clinical assessments were performed on days 0 (pre-treatment), 7, and 14 to monitor pruritus scores using Feline Dermatitis Extent and Severity Index FEDESI, Scoring Feline Allergic Dermatitis (SCORFAD), and Visual analog scale (VAS) scoring systems. SCORFAD and FEDESI assessments were conducted by a veterinary dermatologist, while VAS scoring was completed by pet owners. These scores were recorded to track the clinical progression of the patients.

2.3 Treatment Applications

Cats diagnosed with FASS, including those with secondary infections identified through cytological evaluations, were included in the study. Quercetin (VeNatura, Vefa İlaç, Turkey) was administered orally at a dosage of 3 $mg.kg^{-1}$ once daily for two weeks (Kobayashi et al., 2020). Healthy cats received the same dose of quercetin, and changes during follow-up periods were monitored with blood samples taken for analysis.

2.4 Sampling Procedures

Blood samples (4 mL in total) were collected from the V. *cephalica* antebrachii using lithium-heparinized tubes. Sampling was performed at three time points: before treatment (day 0), on the 7^{th} day of treatment, and on the 14^{th} day of follow-up.

2.5 Laboratory Analyses

Following blood collection, samples were centrifuged at 3,000 rpm for 10 minutes. Plasma was transferred into Eppendorf tubes and stored at -80 °C until analysis. To investigate the changes in oxidative stress caused by pruritus under the influence of quercetin, thiol-disulfide levels were analyzed using ELISA (Rel AssayÒ, Türkiye). Total thiol, native thiol, and disulfide levels were measured. Initially, target antigens or antibodies were added to the microplate and incubated at 4 °C. After washing, a primary antibody was added and incubated at 37 °C. Subsequently, a secondary antibody was introduced and incubated for 1 hour. The plate was washed again, and a substrate was added to observe colour changes. Optical density was measured at 450 nm to determine thiol-disulfide levels.

2.6 Statistical Analyses

Descriptive statistics of the numerical data were conducted. To evaluate the differences between groups and changes over time in response to the administered drug, two-way ANOVA or its non-parametric equivalent, the Kruskal-Wallis ANOVA test, was performed. Statistical analyses were conducted using the GraphPad Prism software (version 9.5.0, Prism).

3 Results and Discussion

The demographic analysis of the study population revealed a total of 8 female and 19 male cats, representing various breeds, with a mean age of 2.48 years. Based on the observed dermatological reaction patterns, the cats were categorized into the following groups: 16 with Head-Neck Pruritus (HNP), 3 with Self-Induced Alopecia (SIA), 2 with Miliary Dermatitis (MD), 3 with Eosinophilic Granuloma Complex (EGC), and 3 with Dermatitis (Table 1). Among the HNP and MD groups, significant reductions were observed in FEDESI, SCORFAD, and VAS scores. In the SIA group, only one cat showed improvement across all clinical scores. Of the three cats in the EGC group, one case diagnosed with linear granuloma exhibited no changes in clinical scores. Clinical assessments revealed that the median FEDESI score decreased from 8 on day 0 to 2 on day 14. Similarly, SCORFAD scores dropped from a median of 4 on day 0 to 2 on day 14. VAS scores, evaluated by the cat owners, also showed a reduction, with median values falling from 5 on day 0 to 1 on day 14. Statistically significant improvements were identified across all scoring parameters (Table 2). An analysis of the thiol-disulfide balance in blood samples collected from healthy and affected cats revealed no statistically significant differences across sampling days. However,

Table 1 Case Classification Based on Skin Reaction Patterns

HNP	SIA	MD	EGC	Dermatitis
n = 16	*n* = 3	*n* = 2	*n* = 3	*n* = 3

HNP – head-neck pruritus, SIA – self-induced alopecia, MD – miliary dermatitis, EGC – eosinophilic granuloma complex

Table 2 Descriptive Statistics of Cats with Atopic Dermatitis Syndrome (FADS)

	Days	FEDESI	SCORFAD	VAS
		n = 27	*n* = 27	*n* = 27
Minimum	0	0.00	1.00	0.00
	7	0.00	0.00	0.00
	14	0.00	0.00	0.00
Maximum	0	35.00	9.00	9.00
	7	32.00	7.00	8.00
	14	32.00	6.00	6.00
Median	0	8	4	5
	7	4	3	3
	14	2	2	1
Mean	0	10.19	4.74	5.00
	7	6.70	3.19	3.19
	14	4.26	1.85	1.78
Standard deviation	0	9.50	2.33	2.18
	7	7.48	2.06	1.98
	14	6.83	1.56	1.99

a mild decrease in both total thiol and disulfide levels was observed in both groups (Table 3).

In our study, demographic factors such as age, gender, breed, and severity of clinical symptoms were evaluated. The mean age of the cats included in the study ranged between 3–5 years, with an even gender distribution observed. Among the cats diagnosed with Feline Atopic Dermatitis Syndrome (FADS), pruritus was detected in 60%, erythema and skin thickening in 40%, and secondary bacterial infections in 30%. These findings were consistent with previous literature (Marsella and De Benedetto, 2017; Mueller, 2020). The demographic data indicated that FADS was more prevalent in specific age and gender groups, particularly in young and middle-aged cats. This suggests that the disease typically begins early in life and follows a chronic course.

In the treatment of atopic dermatitis syndromes (ADS), various strategies such as anti-inflammatory drugs, anti-allergic therapies, immunomodulators, and allergen avoidance are employed (Marsella, 2021). In this study, the clinical symptoms and anamnesis of the cats were meticulously evaluated, and other dermatological diseases were excluded. Intradermal allergy tests, which involve injecting allergens intradermally and observing allergic reactions, are essential in ADS diagnosis (Olivry et al., 2001). However, the unavailability of such tests in our study posed a limiting factor. Additionally, the results of these tests in certain cats were inconclusive, highlighting the need for supplementary diagnostic methods. Skin biopsy was another vital diagnostic tool in ADS. Histopathological examinations revealed microscopic disease characteristics, aiding in the exclusion of other dermatological conditions. Findings such as epidermal hyperplasia, spongiosis, and dermal inflammatory cell infiltration were noted (Scott et al., 2001).

The demographic and clinical features of the cats in our study aligned with findings in the literature. Scott et al. (2001) reported a higher prevalence of ADS in certain breeds and age groups, which was corroborated in our study. Moreover, the literature emphasized that pruritus and skin lesions were the most prominent signs of ADS, significantly impacting the quality of life in affected cats (Olivry and DeBoer, 2001).

Our clinical findings provided important insights into the management of ADS, particularly emphasizing the critical role of addressing pruritus and skin lesions to improve the quality of life in affected cats. Previous studies highlighted the diversity and importance of treatment options, including medications and dietary supplements, in managing ADS (Marsella, 2021). Outside the scope of this study, observations in other animals revealed that immunomodulatory drugs such as corticosteroids and cyclosporine effectively controlled ADS symptoms. However, these treatments often exhibited temporary effects, with frequent relapses. In addition, the potential benefits of natural compounds and plant extracts

Table 3 Thiol-Disulfide Values in Healthy and FASD Cats

Parameter	Days	FATDS	Healthy	P value
TTL (-SH+-S-S-) ($\mu mol.L^{-1}$)	0	189.37 ±8.45	238.86 ±44.12	0.082
	7	184.03 ±3.72	203.34 ±12.82	0.156
	14	184.38 ±4.27	194.55 ±10.41	0.175
NTL (-SH) ($\mu mol.L^{-1}$)	0	117.014 ±5.60	122.51 ±8.38	0.560
	7	122.63 ±6.51	117.42 ±7.08	0.620
	14	120.04 ±5.29	124.77 ±5.62	0.474
Disulfide (-S-S-) ($\mu mol.L^{-1}$)	0	36.17 ±4.56	58.17 ±22.70	0.531
	7	30.69 ±2.60	42.96 ±8.93	0.399
	14	32.16 ±2.53	34.88 ±6.86	0.929
Reduced thiol ratio	0	62.83 ±2.83	58.16 ±7.65	0.682
	7	66.21 ±2.70	59.66 ±5.86	0.399
	14	65.10 ±2.27	65.32 ±4.43	0.789
Oxidized thiol ratio	0	18.58 ±1.41	20.91 ±3.82	0.682
	7	16.89 ±1.35	20.16 ±2.93	0.399
	14	17.44 ±1.13	17.33 ±2.21	0.789
Thiol oxidation reduction ratio	0	457.46 ±76.85	378.27 ±101.42	0.682
	7	696.92 ±257.56	367.79 ±87.42	0.399
	14	522.74 ±129.41	421.80 ±61.22	0.789

in ADS management have been extensively highlighted in the literature and were consistent with findings in our study (Beken et al., 2020; Erden Inal et al., 2001).

Quercetin, a flavonoid with strong antioxidant and anti-inflammatory properties, emerged as a promising therapeutic agent in managing ADS. Its mechanisms of action, including neutralizing free radicals, inhibiting the expression of inflammatory cytokines, and modulating immune responses, aligned with the clinical improvements observed in FADS cats. In our study, quercetin's potential to manage oxidative stress in FADS cats was demonstrated, supported by its ability to regulate cellular redox states via the inhibition of protein disulfide isomerases.

Studies have consistently highlighted quercetin's therapeutic potential in dermatology. Jafarinia et al. (2020) extensively reviewed quercetin's effects on allergic diseases, emphasizing its capacity to mitigate inflammatory responses and oxidative stress. These findings were consistent with the clinical improvements observed with quercetin in our study. Similarly, Lim et al. (2021) demonstrated that quercetin inhibited Propionibacterium acnes-induced skin inflammation, reducing inflammatory responses and cytokine production in skin cells. These mechanisms explained the role of quercetin in alleviating clinical symptoms in FADS cats. The regulatory effects of quercetin on oxidative markers observed in FADS cats aligned with studies showing its ability to reduce lipid peroxidation and strengthen antioxidant defense systems in keratinocytes (Beken et al., 2020).

Additionally, Erden Inal et al. (2001) demonstrated quercetin's ability to mitigate UV-A-induced oxidative damage, underscoring its relevance in skin-related oxidative stress conditions. Experimental models of dermatitis revealed that combining quercetin with *Ginkgo biloba* leaf extract significantly reduced inflammation (Xiao et al., 2023). The synergistic effects of these compounds, achieved through reduced cytokine production and enhanced antioxidant defenses, underscored the potential of combination therapies. These findings highlighted the effectiveness of quercetin in managing inflammatory responses in FADS cats and emphasized the potential benefits of combination treatments.

Chen et al. (2017) reported that quercetin reduced psoriatic-like skin inflammation in mice by inhibiting the NF-κB pathway, suppressing pro-inflammatory cytokine expression, mitigating oxidative stress, and accelerating skin lesion healing. These results supported quercetin's role in reducing inflammatory and oxidative stress markers in FADS cats. Similarly, quercetin has been shown to regulate inflammatory cell activities, including macrophages, T cells, and mast cells, to suppress inflammation (Chirumbolo, 2010). This mechanism explained the clinical improvements observed in our study. Furthermore, quercetin's ability to inhibit mast cell degranulation and histamine release reduced allergic reactions (Kim et al., 2014). This study demonstrated that quercetin could serve as a potential therapeutic agent for managing FADS. Its antioxidant and anti-inflammatory properties effectively alleviated symptoms of atopic dermatitis in cats. Consistent with the literature, the potential application of quercetin in veterinary dermatology was highlighted. Future studies are needed to determine the long-term effects and appropriate dosages of quercetin. This natural compound offers promising outcomes for widespread use in veterinary medicine for FADS-affected cats.

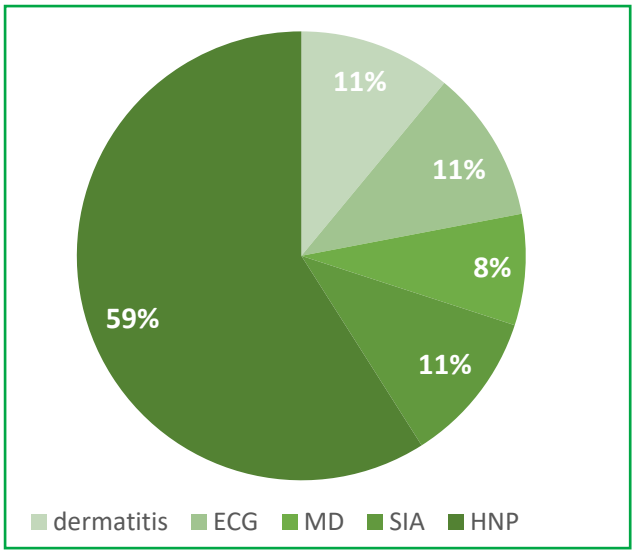

Figure 1 Percentage distribution of skin reaction patterns in the cats included in the study

4 Conclusions

This study suggests that quercetin could be an effective option in the treatment of Feline Atopic Dermatitis Syndrome (FADS). Clinical evaluations revealed significant improvements in the HNP and MD groups, with quercetin showing potential in reducing oxidative stress and alleviating clinical symptoms. Although no significant changes were observed in the thiol-disulfide balance, a mild reduction in total thiol and disulfide levels supports quercetin's antioxidant effects. Quercetin has been shown to modulate inflammation and oxidative stress, thereby reducing symptoms in FADS-affected cats. These findings highlight quercetin as a promising therapeutic alternative in veterinary dermatology. Future studies should focus on determining the long-term effects and optimal dosages of quercetin.

Acknowledgments

This study is a summary of a section from the Master's thesis entitled "Investigation of the Clinical Efficacy of Quercetin in Feline Atopic Dermatitis Syndrome" conducted at the Department of Internal Medicine, Institute of Health Sciences, Aydın Adnan Menderes University. This study was supported by the Scientific Research Projects Unit of Aydın Adnan Menderes University under project number VTF – 24019.

Author contributions

The study was conceived and designed with contributions from all authors: Tunahan Carpan, Ilayda Tendar, Tahir Ozalp, Songül Erdogan, Hasan Erdogan, and Kerem Ural. Data collection and patient follow-up were carried out by Tunahan Carpan under the supervision of Hasan Erdogan. Literature review and preparation of the manuscript were jointly performed by Tunahan Carpan, Ilayda Tendar, Tahir Ozalp, Songül Erdogan, Hasan Erdogan, and Kerem Ural. All aspects of the methodology, data integrity, and analysis were supervised by Hasan Erdogan, Songül Erdogan, and Kerem Ural. Critical revisions of the manuscript were provided by Hasan Erdogan and Kerem Ural. The thesis study, forming the basis of this manuscript, was guided by Hasan Erdogan.

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