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# Evaluation of the Role of Himpyrin Liquid in the Management of Inflammation and Pain in Cats

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**ABSTRACT**

The present study was designed to evaluate *in vivo* efficacy of polyherbal formulation, Himpyrin liquid, for anti-inflammatory, analgesic, and antipyretic activities in cats. Twenty cats with a history of pain, inflammation, and fever due to scratch injuries/accidents were selected (G1; $n = 20$) and supplemented with Himpyrin liquid along with standard treatment until complete recovery. The changes in assessment parameters score, *viz.* pain, fever, and activity level scores, along with adverse effects and product performance/satisfaction scores were evaluated. The results of the present study revealed that pain ($p < 0.01$) and fever ($p < 0.001$) were significantly decreased in cats as early as days 2 and 4, respectively, following Himpyrin liquid supplementation along with standard treatment. The administration of Himpyrin liquid to cats restored the activity level of cats affected with fever and pain due to scratch injuries/accidents. Furthermore, Himpyrin liquid was considered highly satisfactory for inflammation amelioration due to scratch injuries/accidents in cats without any adverse effects. In conclusion, this study supplies considerable preliminary data to hint that Himpyrin liquid possesses anti-inflammatory activities. Hence, Himpyrin liquid at 1 mL twice daily along with standard treatment could be recommended for inflammation amelioration and pain in cats. However, further clinical studies evaluating biochemical parameters were recommended to be carried out to better elucidate the mechanism of action and ultimate impact on the overall health of cats.

**HIGHLIGHTS**

- Himpyrin administration alleviates inflammation and pain in cats and feline.
- Himpyrin liquid possesses anti-inflammatory activities.

**Keywords:** Himpyrin liquid, Cats, Inflammation, Pain, and Polyherbal formulation

Pain in cats has many physiological and emotional negative effects (Hellyer *et al*., 2007). Pain delays recovery, impacts negatively on a patient's wellbeing, and disturbs the bond with its owner and also the veterinary team (Epstein *et al*., 2015; Teixeira *et al.,* 2013). Signs of pain may be subtle and include withdrawing from attention, decreasing mobility, reducing interactions with humans and other animals, poor appetite, and aggression. Chronic pain is pain that has persisted for more than 2–3 weeks, often persists months or years, and may continue beyond the anticipated healing time. Importantly, chronic pain can become dissociated from the inciting cause and be maladaptive, such that the degree of pain does not necessarily correlate with the pathology observed or perceived by the individual, and is not associated with healing (Gowan *et al*., 2011).

Studies have looked at the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for acute, especially perioperative pain in cats (Benito *et al*., 2016; Steagall and Monteiro-Steagall, 2013; Mush *et al*., 2014). Multimodal

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analgesia is commonly advocated, but NSAIDs playing a key role in managing chronic feline pain, especially musculoskeletal pain, is becoming evident just as they do in humans and dogs (Gowan *et al*., 2011; Guillot *et al*., 2013). Although many NSAIDs have been available to treat dogs with degenerative joint disease (Bhathal *et al.,* 2017) only a restricted range has been licensed for short-term (up to a few days) use in cats. Meloxicam, an NSAID, has been licensed for long-term use in cats in many regions of the world, transforming the ability to manage pain in this species, and robenacoxib, another NSAID, has been licensed for up to 6 days of therapy in cats (Gowan *et al*., 2011; Guillot *et al*., 2013). However, adverse drug events related to the use of NSAID most commonly affect the gastrointestinal system, liver, kidneys, and platelet function (Bhathal *et al.,* 2017). While the need for and benefit of NSAID therapy in many situations is clear, screening and monitoring are important for the clinician, owner, and patient to help minimize the likelihood of occurring adverse effects (Ziegler *et al*., 2017).

Persistent long-term use safety concerns must be considered when prescribing these NSAIDs medications for chronic and degenerative pain conditions. Although nonsteroidal medications can be effective, herbs and dietary supplements may offer a safer and often an effective alternative treatment for pain relief, especially for long-term use. Maroon et al. reported the potentially serious side effects of nonsteroidal drugs and commonly used and clinically studied natural alternative anti-inflammatory supplements *viz. Curcuma longa*, green tea, Pycnogenol derived from *Pinus maritima*, *Boswellia serrata* resin, resveratrol derived from *Polygonum cuspidatum*, *Uncaria tomentosa*, *Uncaria guianensis*, and *Capsicum annum* (Ambriz-Perez *et al*., 2016). Also literature study shows the anti-inflammatory activities of herbs namely *Zingiber officinale* (Shin *et al*., 2015). *Cyperus rotundus* (Musta) (Ahmad *et al*., 2014) *Acorus calamus* (Vacha) (Phanse *et al*., 2012) and *Tinospora cordifolia* (Guduchi) (Philip *et al*., 2018).

With this scenario and the growing acceptance of traditional herbal preparations, a polyherbal formulation, Himpyrin liquid, was developed by The Himalaya Drug Company. Moreover, the Himpyrin liquid is claimed to possess anti-inflammatory activities in felines. Hence, *in vivo* efficacy of Himpyrin liquid was assessed in cats in the present study to verify its role in the management of inflammation and pain in cats and felines.

## MATERIALS AND METHODS

### Polyherbal formulation

Himpyrin liquid is a proprietary polyherbal formulation developed by The Himalaya Drug Company, Bengaluru, India, composed of *Z. officinale*, *C. rotundus*, *A. calamus*, *G. glabra*, and *T. cordifolia.*

### Ethical committee approval

The present study was conducted following the guidelines laid down for the care and use of animals. Moreover, the study protocol was approved by the Institutional Animal Ethics committee, The Himalaya Drug Company, Bangalore (protocol no. AHP/SA/10/18).

### Study subjects

Twenty cats with a history of pain, inflammation, and fever due to scratch injuries/accidents were presented at the Vet Medix Clinic, Bengaluru, Karnataka, and enrolled in the current study. The study details, treatment plan, outcomes, and other pros and consequences were explained to the pet owner. In addition, consent was obtained before study enrollment.

### Study design and experimental details

Twenty cats with a history of pain, inflammation, and fever due to scratch injuries/accidents were selected (G1; $n$ = 20) and supplemented with Himpyrin liquid along with standard treatment until complete recovery. Cats were administered with subcutaneous Convenia injection at a dose of 3.6 mg/lb (8 mg/kg) body weight based on the severity of pain and fever. Concurrently, crusts due to injury on the skin were gently removed with a brush and cleaned with sterile saline solution and wiped with dry sterile cotton. Concurrent treatment with other analgesics, antipyretic, and anti-inflammatory supplements was discontinued when Himpyrin liquid is being administered to the cats.

### Evaluation of study parameters

The changes in assessment parameters score, *viz.* pain, fever, and activity level scores, along with adverse effects and product performance/satisfaction scores were evaluated following Himpyrin liquid supplementation to access the role of Himpyrin liquid in the management of inflammatory conditions in cats according to the grading system (Taraphdar *et al*., 2018) described in Table 1.

**Table 1: Assessment Parameters Grading System**

| Parameter | Description | Score |
|---|---|---|
| Fever | Normal body temperature, 100.4 °F to 102.5 °F | 0 |
| | Abnormal body temperature, ≥102.5 °F | 1 |
| Pain | *Normal:* No pain, no overt signs of discomfort, and no resentment to firm pressure | 0 |
| | *Mild pain:* No overt signs of discomfort but resentment to firm pressure | 1 |
| | *Moderate pain:* Some overt signs of discomfort which are made worse by firm pressure | 2 |
| | *Severe pain:* Obvious sign of persistent discomfort which are made worse by firm pressure | 3 |
| Activity level | *Normal:* Active and alert | 0 |
| | Dull and depressed | 1 |
| | Sluggish and lethargy | 2 |
| Activity level | Absent | 0 |
| | Present | 1 |
| Product performance/ Satisfaction score | Highly satisfied | 4 |
| | Moderately satisfied | 3 |
| | Neither satisfied nor dissatisfied | 2 |
| | Not satisfied (no relief) | 1 |

### Statistical analysis

The data are expressed as mean ± standard error of the mean (SEM). Data were subjected to a two-way analysis of variance followed by the Bonferroni test to draw the comparison between day 1 and the remaining treatment days. In addition, $p \leq 0.05$ was considered statistically significant.

## RESULTS AND DISCUSSION

Pain ($p < 0.01$) and fever ($p < 0.001$) was significantly decreased in cats as early as days 2 and 4, respectively, following Himpyrin liquid supplementation along with standard treatment. However, complete alleviation of pain and fever was observed on day 5. The activity level score (mean ± SEM) exhibited by animals on day 1 was 1.50 ± 0.18. However, animals showed a statistically significant ($p < 0.001$) improvement in activity level score as early as day 2 onwards compared with day 1 following Himpyrin liquid supplementation along with standard treatment and restored to normal (0.00 ± 0.00) on day 5. The activity level score revealed that 5 days of Himpyrin liquid supplementation along with standard treatment is required for complete restoration of the activity level of cats with fever and pain due to scratch injuries/accidents (Table 2). The adverse effects and product performance/satisfaction scores of Himpyrin liquid were 0.00 ± 0.00 and 3.75 ± 0.10, respectively (Table 3).

These findings depicted that Himpyrin liquid was considered highly satisfactory for inflammation amelioration due to scratch injuries/accidents in cats. These findings could be attributed to the anti-inflammatory activities of Himpyrin liquid. Furthermore, Himpyrin liquid supplementation in cats has no adverse effects indicating that ingredients used in the products are safe for oral supplementation in cats.

The anti-inflammatory activities of Himpyrin liquid could be understood by individual herbal ingredients, *viz. Z. officinale*, *C. rotundus*, *A. calamus*, *G. glabra*, and *T. cordifolia* present in the Himpyrin liquid. Moreover, Hassan et al. reported that gingerol, shogaol, and other structurally related substances in ginger inhibit prostaglandin and leukotriene biosynthesis through suppression of 5-lipoxygenase or prostaglandin synthetase. Additionally, they can also inhibit the synthesis of proinflammatory cytokines (e.g., interleukin (IL)-1, tumor necrosis factor-α (TNF-α), and IL-8) (Rahmani, 2014; Jafarnejad *et al*., 2017). The paw edema in carrageenan-induced rats was considerably reduced by treating with 400 mg/kg aqueous ginger extracts when compared with untreated rats ($p < 0.001$). Hence, the investigations of Hassan et al. showed that the aqueous extract of *Z. officinale* possesses anti-inflammatory properties (Hassan, *et al*., 2017).

Fulgidic acid from the rhizomes of *C. rotundus* and the underlying mechanisms involved in its anti-inflammatory activity was evaluated by Shin *et al.* (2015) The results revealed that fulgidic acid reduced the production of nitric oxide, prostaglandin E2, TNF-α, and IL-6

**Table 2:** Effect of Himpyrin Liquid on Assessment Parameters in Cats

| Parameter | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 |
|---|---|---|---|---|---|
| **Fever score** | 0.85 ± 0.08 | 0.85 ± 0.08 | 0.60 ± 0.11 | ***0.20 ± 0.09 | ***0.00 ± 0.00 |
| **Pain score** | 2.25 ± 0.24 | **1.80 ± 0.25 | ***1.10 ± 0.18 | ***0.35 ± 0.11 | ***0.00 ± 0.00 |
| **Activity level score** | 1.50 ± 0.18 | ***1.00 ± 0.16 | ***0.70 ± 0.11 | ***0.25 ± 0.10 | ***0.00 ± 0.00 |

Values are expressed as mean ± SEM; $n = 20$; **$p < 0.01$ and ***$p < 0.001$ compared with day 1 based on repeated-measures two-way analysis of variance followed by the Bonferroni test.

**Table 3:** Effect of Himpyrin Liquid on Adverse Effect and Product Performance Score in Cats

| Parameter | Score |
|---|---|
| Adverse effects | 0.00 ± 0.00 |
| Product performance/product satisfaction | 3.75 ± 0.10 |

Values are expressed as mean ± SEM; $n = 20$.

in lipopolysaccharide (LPS)-induced RAW264.7 macrophages. In addition, fulgidic acid suppressed the LPS-induced expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) at the protein level, as well as iNOS, COX-2, TNF-α, and IL-6 at mRNA levels. Furthermore, fulgidic acid suppressed the LPS-induced transcriptional activity of activator protein-1 (AP-1) as well as the phosphorylation of c-Fos and c-Jun. In addition, fulgidic acid did not show any effect on LPS-induced nuclear factor κB activity. In summary, these results suggest that the anti-inflammatory effect of fulgidic acid was associated with the suppression of iNOS, COX-2, TNF-α, and IL-6 expressions through downregulating AP-1 activation in LPS-induced RAW264.7 macrophages (Shin *et al*., 2015). In another study reported by Ahmad *et al.,* (2014) the crude extract of *C. rotundus* was analyzed for anti-inflammatory activity. The results revealed that at 300 and 500 mg/kg doses of crude extract *C. rotundus* was more effective at 2 and 4 h, respectively. The maximum percentage of inhibition (36%) observed with a 500 mg/kg dose. The findings of this study showed that protection from edema and pain was evident following supplementation of crude extract of *C. rotundus* (Ahmad *et al*., 2014).

A preclinical study evaluating the anti-inflammatory activity of the chloroform extract of *T. cordifolia* (Willd.) conducted by Philip *et al*. reported that the LPS-induced upregulation of proinflammatory biomarkers was significantly inhibited by the chloroform extract of *T. cordifolia* without inhibiting COX-1. The chloroform extract of *T. cordifolia* and LPS-incubated cells showed reduced phosphorylated p38 MAPK levels, and higher levels of NF-κB were retained in the cytoplasm. Furthermore, rats pretreated with chloroform extract of *T. cordifolia* showed a statistically significant decrease in paw edema ($p \leq 0.05$) (Philip *et al*., 2018).

A review published by Phanse *et al.* (2012) reported that *A. calamus* leaf extract inhibits the production of proinflammatory cytokines through multiple mechanisms and could be considered as a novel and effective anti-inflammatory agent (Phanse *et al*., 2012). Furthermore, another study evaluating the anti-inflammatory activity of 80% ethanolic extract of *A. calamus* Linn. leaves in albino rats using the carrageenan-induced paw edema and cotton pellet granuloma tests revealed that 80% ethanolic extract of *A. calamus* at the dose levels of 100 and 200 mg/kg caused a significant ($p < 0.05$) reduction in the paw edema in rats. These findings delineated that the 80% ethanolic extract of *A. calamus* leaves possesses anti-inflammatory activity probably through the reduction of various biochemicals, *viz.* histamine, 5-HT, and various kinases which are involved in the early inflammation phases (Jain *et al*., 2010).

## CONCLUSION

In conclusion, this study delineated that cats and feline suffering from inflammation and pain due to scratch injuries/accidents were ameliorated following Himpyrin liquid administration. Hence, this supplies considerable preliminary data to hint that Himpyrin liquid possesses

anti-inflammatory activities. However, further clinical study evaluating biochemical parameters is recommended to better elucidate the mechanism of action and ultimate impact on the overall health of cats.

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