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Morphine versus apigenin-induced antinociception in rodent models- A randomised comparative study

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Abstract

Apigenin a plant-derived flavone with anti-inflammatory and antioxidant properties. Therefore, it is of interest to evaluate the antinociceptive activities in the acetic acid-induced writhing test in the rats and compared with morphine while assessing opioid receptor involvement using naloxone. Twenty-four Wistar rats were divided into four groups (n = 6): control, morphine (5 mg/kg, S.C.), apigenin (20 mg/kg, p.o.), and naloxone (5 mg/kg, i.p.) plus apigenin, and writhing responses were recorded 5–20 min after intraperitoneal injection of 0.6% acetic acid. Morphine significantly reduced writhing counts at all-time points compared with control ($p < 0.001$), whereas apigenin produced modest antinociceptive activity and the naloxone + apigenin group showed intermediate effects. Repeated-measures and one-way ANOVA demonstrated significant within and between group differences ($p < 0.001$). Thus, data shows that apigenin exerts mild antinociceptive effects that are largely independent of predominant μ -opioid receptor mediation.

Keywords: Apigenin, antinociception, visceral pain, acetic acid-induced writhing**Background**

Pain is one of the most common reasons people seek medical care and represents a major public health concern. Chronic pain affects around 20–30% of adults worldwide, representing a major source of disability, psychological distress and economic strain [1, 2]. Population-based studies from India reveal a likewise high prevalence of chronic pain, affecting roughly one-fifth to over one-third of adults and highlights to show, it often remains inadequately managed [3, 4]. Despite the advancement of multimodal analgesic techniques, management of acute and chronic pain remains inadequate in numerous contexts, highlighting the necessity for safer and more effective analgesic approaches [5, 6]. Opioid medications are mainstream therapeutic agents employed in managing moderate to severe nociceptive pain [7]. Morphine, a quintessential μ -opioid receptor agonist, remains the benchmark for the treatment of severe acute pain and cancer-associated pain [8]. The clinical efficacy of morphine and other powerful opioids is constrained by side effects including respiratory depression, constipation, nausea, tolerance, physical dependency and the potential for misuse and opioid use disorder [9]. There are growing concerns about opioid-related problems and evolving prescribing guidelines have intensified interest in alternative non-opioid and opioid-sparing strategies for pain management [10]. Natural products continue to be a significant source of novel analgesic candidates [11]. Flavonoids, a class of polyphenolic chemicals widely present in fruits, vegetables and medicinal plants, have attracted a lot of interest due to their potential anti-inflammatory and antinociceptive characteristics [12, 13]. A systematic analysis revealed several flavonoids exhibiting consistent analgesic effects in preclinical animal models, functioning through numerous pathways such as the suppression of pro-inflammatory mediators, control of oxidative stress and modulation of central neurotransmitter systems [14]. The

observations substantiate the concept that specific flavonoids may function as templates for the creation of safer analgesic drugs or adjuncts to current regimens [15]. Apigenin (4', 5, 7-trihydroxyflavone) is a naturally occurring flavone found in several dietary plants such as chamomile, parsley and celery [16]. Experimental research has shown that apigenin possesses anti-inflammatory, antioxidant, neuroprotective and antitumor properties [17]. In rodent nociceptive models, apigenin extracted from the marine red algae, *Acanthophoraspicifera*, showed substantial antinociceptive effects in the hot-plate, tail-immersion and acetic acid-induced writhing assays, as well as suppression of carrageenan-induced paw edema and granuloma formation [18]. Off-late, an experimental study in rodents showed a dose-dependent analgesic effect of apigenin, comparable to that of standard non-steroidal and centrally acting analgesics, thereby reinforcing its promise as a potential analgesic agent [19]. However, the precise mechanisms underlying apigenin-induced antinociception remain incompletely defined and the possible contribution of opioid pathways has not been fully clarified [20]. Naloxone is a competitive opioid receptor antagonist with high affinity for μ -opioid receptors and is widely used to reverse opioid-induced respiratory depression and other central effects [21, 22]. By displacing opioid agonists from μ -receptors, without producing intrinsic analgesic activity, naloxone is also employed experimentally to probe the involvement of endogenous or exogenous opioid mechanisms in behavioural and pharmacological responses [23]. Demonstrations that naloxone, attenuates or abolishes the antinociceptive effect of a test compound is commonly interpreted as evidence for an opioid-mediated component of its potent action [24]. Therefore, it is of interest to evaluate the antinociceptive effect of apigenin in rodent and to compare its efficacy with morphine.

Materials and Methods:

Study design:

This was an *in vivo*, randomized, controlled experimental study with four parallel treatment groups and repeated measurements over time. A total of 24 healthy adult Wistar albino rats (either sex, 150–200 g) were used and allocated to four groups (n = 6 per group):

- [1] **Group-I:** Control - Normal saline (0.9% NaCl, per oral (p.o.).
- [2] **Group-II:** Standard - Morphine sulfate 5 mg/kg, subcutaneous (s.c.).
- [3] **Group-III:** Apigenin 20 mg/kg, per oral (p.o.).
- [4] **Group-IV:** Naloxone hydrochloride 5 mg/kg, i.p. + Apigenin 20 mg/kg, p.o.

The primary outcome was the nociceptive response, measured as the number of abdominal constrictions (writhes) at pre-defined time points following a chemical nociceptive stimulus.

Animals and housing:

Animals were procured from the institutional animal facility and acclimatised for at least 7 days before experimentation. Rats were housed in polypropylene cages with sterile rice-husk bedding, under controlled environmental conditions (temperature $22 \pm 2^\circ\text{C}$, relative humidity 50–60%, 12:12 h light-dark cycle). Standard pelleted laboratory chow and water were provided *ad libitum*. Animals were fasted for 12 hrs. before the experiment with free access to water. All procedures conformed to the “Guide for the Care and Use of Laboratory Animals, 8th edition” [25, 26] and the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines for laboratory animal facility [27, 28]. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) constituted under CPCSEA (approval no. 1919/GO/Re/S/16/CPCSEA) on 14/12/2018.

Drugs and chemicals:

Apigenin ($\geq 98\%$ purity, Sigma-Aldrich, St. Louis, MO, USA) was suspended freshly each day in 0.5% Carboxymethylcellulose (CMC) in distilled water for oral administration (p.o.). Morphine sulfate injection (5 mg/mL; Neon Laboratories, Mumbai, India) was diluted with normal saline for subcutaneous (S.C.) use. Naloxone hydrochloride injection (0.4 mg/mL; Samarth Life Sciences, Mumbai, India) was diluted with normal saline for intraperitoneal (i.p.) administration. Glacial acetic acid (analytical reagent grade; Merck, Darmstadt, Germany) was used to prepare a 0.6% v/v solution in distilled water for induction of writhing. Normal saline (0.9% NaCl; Baxter India, Gurgaon, India) was used as vehicle for i.p. and S.C. injections. All doses are expressed as mg/kg body weight and the injection volume was maintained at 10 ml/kg for all groups.

Experimental procedure:

Randomisation and dosing:

On the day of the experiment, rats were weighed and randomly allocated to one of the four treatment groups using a computer-generated random number list. Each animal received a single

dose of the assigned treatment as follows: apigenin (20 mg/kg, p.o.) in Groups III and IV; morphine (5 mg/kg, s.c.) in Group II; naloxone (5 mg/kg, i.p.) in Group IV; and equivalent volume of vehicle (normal saline or 0.5% CMC) in Group I. Apigenin and vehicle were administered 60 min before nociceptive testing, whereas morphine and naloxone were administered 30 min before the test.

Acetic acid-induced writhing test:

Peripheral antinociceptive activity was assessed using the acetic acid-induced writhing test as initially described by Baramaki *et al.* [29] with minor modifications. Briefly, 0.6% v/v acetic acid solution (10 ml /kg, i.p.) was injected into the lower right quadrant of the abdomen 30 or 60 min after drug/vehicle administration, as per the dosing schedule above. Following acetic acid injection, each rat was placed individually under a transparent observation chamber. After a 5-minutes latency period, the number of characteristic abdominal constrictions (“writhes”: contraction of abdominal muscles accompanied by stretching of the hind limbs) was counted by an observer blinded to group allocation. Writhes were recorded during four consecutive 5minutes observation periods up to 20 minutes. For statistical analysis, the cumulative number of writhes at 5, 10, 15 and 20 min was used as repeated measures for each animal.

Data collection:

Data for each rat (animal ID, group assignment, body weight and number of writhes at 5, 10, 15 and 20 min) were recorded in predesigned case record forms at the time of observation by the same trained observer to minimise inter-observer variability. The data were subsequently entered into a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) and cross-checked for transcription errors by a second investigator before statistical analysis.

Statistical analysis:

Nociceptive responses are expressed as mean $\pm$ standard deviation (SD) for six animals in each group (n = 6). Within-group changes in writhing counts over time (5, 10, 15 and 20 minutes) were analysed using one-way repeated-measures analysis of variance (ANOVA) separately for each group, with time as the within-subject factor. Between-group differences at each time point were analysed using one-way ANOVA with treatment group as the fixed factor. When ANOVA indicated significance, Tukey’s honest significant difference post hoc test was applied for multiple pairwise comparisons. All tests were two-tailed and p-values < 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA) and cross-checked using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA).

Results:

A total of 24 rats were divided equally into four groups: Group-I (Control-normal saline), Group-II (Morphine 5 mg/kg, S.C.), Group-III (Apigenin 20 mg/kg, orally) and Group-IV (Naloxone

5 mg/kg, i.p. + Apigenin 20 mg/kg, orally). Nociceptive responses were recorded at 5, 10, 15 and 20 minutes after treatment (**Table 1 and Figure 1, 2**). Repeated-measures ANOVA on all animals showed a significant main effect of time on nociceptive scores ($F(3, 69)=57.83, p<0.001$). When analysed within each treatment group separately, time had a significant effect in Group-I, Group-II, Group-III and Group-IV (all $p<0.001$)

Table 1: Time course of nociceptive response (mean number of writhes) in different treatment groups (n = 6 per group)

Group	5 min (mean ± SD)	10 min (mean ± SD)	15 min (mean ± SD)	20 min (mean ± SD)
Group-I (Control-NS)	14.50 ± 0.55	22.67 ± 2.07	30.33 ± 1.37	36.83 ± 1.83
Group-II (Morphine 5 mg/kg, s.c.)	1.50 ± 0.55	2.83 ± 0.41	4.00 ± 0.63	4.67 ± 0.52
Group-III (Apigenin 20 mg/kg, orally)	12.83 ± 0.75	21.83 ± 1.72	30.33 ± 1.21	34.67 ± 1.37
Group-IV (Naloxone 5 mg/kg, i.p. + Apigenin 20 mg/kg, orally)	10.50 ± 1.05	14.67 ± 0.52	17.00 ± 0.63	18.83 ± 1.17

Values are expressed as mean ± standard deviation (SD); n = 6 rats per group.

Table 2: Repeated-measures ANOVA for the effect of time on nociceptive scores

Analysis	F value	p-value
Group-I (Control-NS)	219.67	<0.001
Group-II (Morphine 5 mg/kg, s.c.)	104.50	<0.001
Group-III (Apigenin 20 mg/kg, orally)	305.36	<0.001
Group-IV (Naloxone + Apigenin)	142.55	<0.001

Repeated-measures ANOVA with Time (4 levels: 5, 10, 15 and 20 minutes) as the within-subject factor.

Table 3: One-way ANOVA for between-group differences at each time point

Time point	F value (df = 3, 20)	p-value
5 min	355.29	<0.001
10 min	263.59	<0.001
15 min	924.89	<0.001
20 min	790.71	<0.001

One-way ANOVA with Group (4 levels) as the between-subject factor at each time point

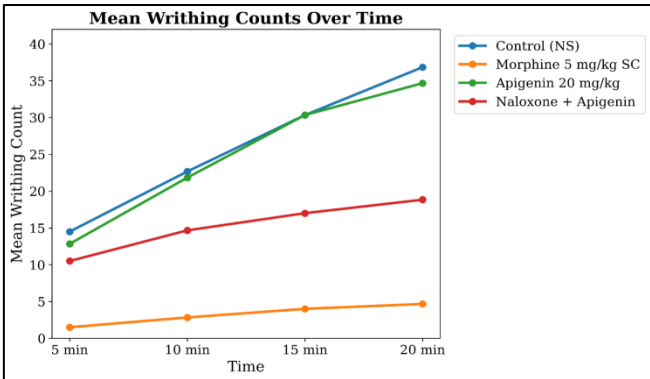


Figure 1: Time course of nociceptive response (mean number of writhes) in different treatment groups (n=6 per group)

Discussion:

The present study evaluated the antinociceptive effect of apigenin in an acetic acid-induced writhing model in rats and explored the possible involvement of opioid pathways using naloxone. The robust inhibition of writhing produced by morphine confirmed the sensitivity of the model to standard opioid analgesia and supports its suitability for assessing peripheral visceral pain responses primarily mediated by prostaglandins, bradykinin and other inflammatory mediators [30, 31]. Apigenin at 20 mg/kg (p.o.) produced only a modest decrease in writhing frequency versus the control group, with statistically significant mean differences observed only at all-

(**Table 2**). Independent one-way ANOVA performed at each time point showed highly significant differences among the four groups at 5, 10, 15 and 20 minutes (all $p<0.001$; **Table 3**). Across all time points, mean nociceptive scores were numerically highest in Group-I and Group-III, intermediate in Group-IV and lowest in Group-II (**Tables 1 and 3, Figure 3**).

time points. This magnitude of effect is smaller than that reported in the previous experimental rodent studies, in which

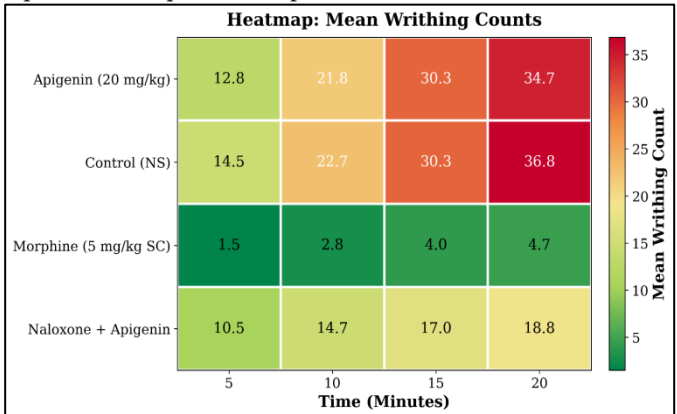


Figure 2: Effectively illustrates the mean writhing counts of various treatment groups across different time points

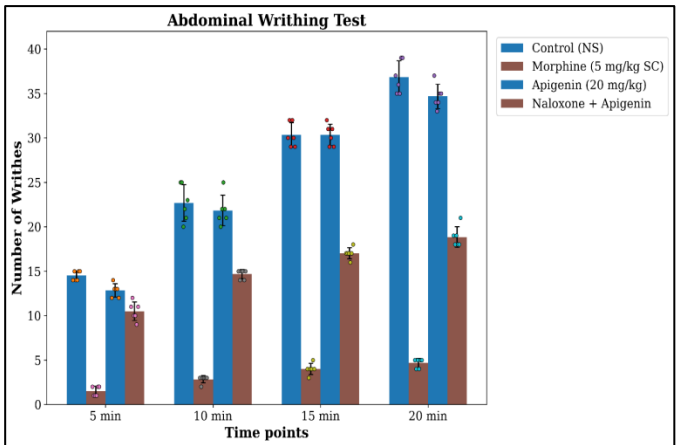


Figure 3: Comparison of number of writhes of various treatment groups across different time points with error bars

apigenin or its derivatives showed pronounced antinociception across several experimental rodent models, including the acetic acid writhing, hot-plate and formalin tests [32, 33]. The plausible explanations for this deviation may include interspecies differences (rat vs mouse), variations in the route of administration (oral vs intraperitoneal), the use of a single-dose

regimen and differences in vehicle or formulation that could influence bioavailability. The acetic acid-induced writhing test mainly measures pain relief through peripheral mechanisms. If apigenin acts more strongly through central (brain and spinal cord) pathways, this model may not fully capture its analgesic effect and could therefore underestimate its true efficacy [29]. The combination of naloxone (5 mg/kg, i.p.) with apigenin resulted in greater inhibition of writhing than apigenin alone, although still clearly inferior to morphine. This pattern does not fit the classic expectation that naloxone would abolish an opioid receptor-mediated effect. In contrast, previous work with apigenin-containing extracts has shown that naloxone significantly attenuated their antinociceptive activity, suggesting participation of opioid and cholinergic systems [32]. Flavonoids structurally related to apigenin have been shown to bind opioid receptors *in vitro* and to exhibit naloxone-sensitive antinociception *in vivo*, [34] but the present findings do not provide strong evidence that μ -opioid receptor activation is the dominant mechanism at the dose level and tested routes. One possible explanation is that the naloxone-apigenin combination engages additional non-opioid pathways. Beyond their role as classical opioid antagonists, naloxone and related compounds can modulate toll-like receptor 4 (TLR4) and glial signalling and, at low doses, have been reported to modify inflammatory and hyperanalgesic responses in a bidirectional manner [35]. In parallel, apigenin is well documented to exert anti-inflammatory and antioxidant actions by inhibiting NF- κ B signalling and down-regulating the production of pro-inflammatory cytokines and mediators [16]. The intermediate analgesic effect seen with naloxone plus apigenin combination may therefore reflect a complex interplay between peripheral anti-inflammatory effects of apigenin and modulatory actions of naloxone on inflammatory or glial pathways, rather than pure antagonism at μ -opioid receptors. However, this remains speculative in the absence of experimental assays. Taken together, the findings support the view that apigenin possesses measurable, but relatively weak, peripheral antinociceptive activity in this acute visceral pain model and that its effect is clearly inferior to that of morphine at the doses tested [36]. The lack of straightforward reversal by naloxone suggests that any opioid receptor-mediated contribution is limited under these conditions and those non-opioid mechanisms, most plausibly anti-inflammatory and antioxidant actions are likely to predominate [23]. Several limitations should be considered when interpreting these results. The sample size was modest ($n = 6$ per group) and only a single dose and route of administration were evaluated for apigenin and naloxone, precluding dose-response analysis and pharmacodynamic modelling. Only one acute nociceptive model was used; no central pain assays (e.g., hot-plate, tail-flick or formalin test) or chronic inflammatory or neuropathic models were included, limiting inferences about central vs peripheral actions or long-term efficacy [12, 36]. Mechanistic endpoints such as measurement of prostaglandins, cytokines or NF- κ B activity were not undertaken, so the proposed anti-inflammatory mechanisms remain indirect. Finally, as with all rodent experiments, extrapolation to human analgesic efficacy is

constrained by interspecies differences in pharmacokinetics, pharmacodynamics and pain-processing pathways [17]. Future research will concentrate on a broader range of apigenin doses, alternative formulations to optimise oral bioavailability and evaluation in complementary nociceptive models, including central and chronic pain paradigms. Incorporating selective μ -, δ - and κ -opioid receptor antagonists, as well as TLR4 or glial modulators, could help clarify the relative contribution of opioid and non-opioid pathways. Parallel assessment of inflammatory mediators and oxidative stress markers would allow better linkage between behavioural and molecular effects.

Conclusion:

Apigenin showed modest antinociceptive activity in the acetic acid-induced writhing test, but morphine showed markedly greater analgesic efficacy. Naloxone did not completely abolish apigenin's analgesic effect, suggesting that its action is unlikely to be mediated predominantly through μ -opioid receptors. It should be noted that further investigation of apigenin as a potential adjunctive analgesic with detailed mechanistic and translational studies are required before clinical application.

Abbreviations:

- [1] NS – Normal saline
- [2] CMC – Carboxymethylcellulose
- [3] i.p. – Intraperitoneal
- [4] s.c. – Subcutaneous
- [5] p.o. – Per os (oral)
- [6] IAEC – Institutional Animal Ethics Committee
- [7] CPCSEA – Committee for the Purpose of Control and Supervision of Experiments on Animals
- [8] SD – Standard deviation
- [9] ANOVA – Analysis of variance
- [10] SPSS – Statistical Package for the Social Sciences
- [11] TLR4 – Toll-like receptor 4
- [12] NF- κ B – Nuclear factor kappa B

Conflicts of interest:

The authors declare that there are no conflicts of interest regarding the publication of this article.

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