



Pharmacodynamic and Pharmacokinetic Comparison between Selective and Non-selective COX-2 Inhibitors in Mice

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ABSTRACT

Nowadays, there is a need for good and efficacious NSAIDs with minimal side effects to be applied in veterinary medicine. The aim was to compare the pharmacodynamics (analgesia and inhibition of COX-2) and pharmacokinetics between selective (nimesulide) and non-selective (aspirin) COX-2 inhibitors in mice. Assessing the median effective doses by using the up-and-down method, COX-2 activity and plasma concentrations for both nimesulide and aspirin with their pharmacokinetic profiles in mice. The median effective doses (ED50s) of nimesulide and aspirin were found to be 7.9 and 212.23 mg/kg, respectively, using the hot-plate. Both nimesulide (15.8 mg/kg, i.m.) and aspirin (424.5 mg/kg, i.m.) inhibited COX-2 activity through a decrease in COX-2 concentrations in the plasma, liver, and kidney of mice, with superior inhibition when administering nimesulide in comparison to the control (negative and positive) and aspirin-treated groups. Plasma concentrations of nimesulide (15.8 mg/kg, i.m.) measured for different comparable periods of 0.5, 1, 2, 4, and 24 hours were higher than those of aspirin, which were 14.62, 9.22, 9.88, 7.38 and 2.27 µg/ml, respectively, while aspirin (424.5 mg/kg, i.m.) was 4.35, 3.17, 2.54, 2.25 and 1.21 µg/ml, at the same measured times. Nimesulide pharmacokinetic variables were estimated to be AUC_{0-∞} 169.18, AUMC_{0-∞} 2358.72, K_{el} 0.06, C_{max} 14.62, T_{max} 0.5, t_{1/2β} 11.07, MRT 13.94, V_{ss} 1.49, and Cl 0.09, while aspirin pharmacokinetic parameters differed to be 82.31, 2428.32, 0.03, 4.35, 0.5, 21.25, 158.12, and 5.16, respectively. The study concluded that nimesulide has superior pharmacological properties (analgesic, antipyretic, and anti-inflammatory) than aspirin due to its ability to inhibit COX-2 more selectively and its unique pharmacokinetics in mice, which may be useful in veterinary medicine.

Keywords: Aspirin, COX-2, Mice, Nimesulide, Pharmacokinetics.

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INTRODUCTION

Nimesulide has a chemical name of 4-nitro-2-phenoxyethanesulfonamide and is one of the famous drugs belonging to the non-steroidal anti-inflammatory medications that inhibit prostaglandin (PG) biosynthesis through selective cyclooxygenase (COX)-2 inhibition. The enzyme COX existed as two isoforms, COX-1 and COX-2. Nimesulide was a better inhibitor for COX-2, with 20 times more selectivity than COX-1 (Balaji *et al.*, 2013).

Nimesulide is commonly used for medical management of arthritis, pain, and fever with a relatively low risk for gastrointestinal side effects, as demonstrated by numerous clinical trials (Hemmateenejad *et al.*, 2008; David *et al.*, 2013). Nimesulide also inhibits the release of oxidizers produced by neutrophils, decreasing the release of histamine synthesized by mast cells. The other benefit

of using nimesulide was the scavenging of hypochloric acid, which contributes to the apoptotic process and has antioxidant properties. On the other hand, aspirin (acetylsalicylic acid) has been used as a drug for over 10 decades for its analgesic, antipyretic, and anti-inflammatory properties of NSAIDs. Aspirin exerts its pharmacological action by inhibiting the production of PGs (Kress *et al.*, 2016).

The conversion of arachidonic acid to PG occurs by COX to produce the PGH₂ subtype (which is a precursor to the other PGs). Also, both COX-1 (constitutive) and COX-2 (inducible) isoforms are involved in aspirin action by binding covalently, which will lead to irreversible inhibition of COX action, unlike other NSAIDs that bind reversibly with COX (Kanani *et al.*, 2015; Kwon *et al.*, 2019). Inhibition of platelet aggregation resulted from the reduction of COX-1, while a decrease in COX-2 activity leads to

analgesic, antipyretic, and anti-inflammatory actions (Patrick *et al.*, 2015).

The present study was designed to compare the pharmacodynamics (analgesic efficacy with the degree of COX-2 inhibition) and pharmacokinetics between nimesulide (a selective COX-2 inhibitor) and aspirin (a non-selective COX-2 inhibitor) in mice.

MATERIALS AND METHODS

Ethical considerations

The study was approved via the animal use and care committee at the Veterinary Medicine College /Mosul University (UM.VET.2022.076).

The animals and drug preparation

Male and female albino Swiss mice weighing between 26-30 g were placed under a standard condition of 10/14 hours light/dark cycle at 22 °C. The water and food available in the laboratory to mice received humane care. Nimesulide injectable solution (10%, Instant Pharmaceuticals, India) and aspirin pure powder (Sanofi, France). The drugs were diluted with normal saline to get the required dosage applied for intramuscular (i.m.) injection in mice with a 5 ml/kg as a volume of injection (Mohammed *et al.*, 2022).

Determination of individual ED₅₀s for nimesulide and aspirin in mice

The ED₅₀ of nimesulide and aspirin was determined by using the up-and-down method (Dixon, 1980). Nociception was measured using a hot plate (thermal method) (DLAB, Germany) adjusted to 56 °C. Every single mouse was placed on the hot plate, and the time of nociception was recorded as licking of the fore or hind paw or/and jumping off from the surface in seconds (pre-treatment). Nimesulide or aspirin was administered as an initial dose (10 and 100 mg/kg, i.m., respectively). The initial dose was determined depending on the previous studies (Pong *et al.*, 1985). The increase and decrease in the later dose of each drug were at a constant value (Al-Zubaidy *et al.*, 2011; Mohammad *et al.*, 2012; Mousa *et al.*, 2019). Thirty minutes after the injection of the drug, the recording of the time for the nociceptive response (post-injection of the selected drug) was also recorded (Mousa and Mohammad, 2012; Mousa *et al.*, 2021). If the post-treatment nociceptive time response was greater than the pre-injection one, that means analgesia; otherwise, the drug has not. The mice will be left on the hot plate for a maximal period of 20 seconds to avoid paw's tissue injury (Pong *et al.*, 1985; Mousa, 2020; 2021).

Nimesulide and aspirin: A comparative inhibition of COX-2 concentration in plasma, liver and kidney in mice

This experiment included 6 groups of mice (5 mice per group). Normal saline was injected i.p. into

the negative control group. The nimesulide-treated group received a dosage of 15.8 mg/kg, i.m., while aspirin was injected at 424.5 mg/kg, i.m. The positive group was treated with acetic acid 1% (0.1 ml/10 g) i.p. for induction of COX-2, nimesulide (15.8 mg/kg i.m.) + acetic acid, whereas the last group was treated with aspirin (424.5 mg/kg i.m.) + acetic acid. We collected blood samples after 30 minutes after treatment with the drugs, then obtained plasma and isolated liver and kidney were used to estimate the COX-2 activity by using the enzyme-linked immunosorbent assay (ELISA) technique done by a specified ELISA gear (catalogue number SL0731Mo, China) to examine the COX-2 concentration in pictograms (pg)/ml. The drug absorbance was assessed on 450 nm of COX-2 standards. Simple linear regression was produced by the standard calibration curve, which was $y = 0.1034 + 0.0022x$ (correlation coefficient (R²)) of 0.9988 (Fig. 1) (Alias *et al.*, 2011; Caiazzo *et al.*, 2019). We measured the concentration of COX-2 in the plasma by collecting the blood in specified tubes containing EDTA as an anticoagulant which undergoes incubation at room temperature for 10–20 minutes. The centrifuged tubes (3000 rpm for 20 min) were then collected carefully as plasma samples. Liver and kidney samples were obtained by cutting, weighing, and freezing the tissues at -20 °C, then homogenized after adding PBS (pH 7.4) at 4 °C. The supernatant was centrifuged at 3000 rpm for 20 min and then applied for an ELISA assay.

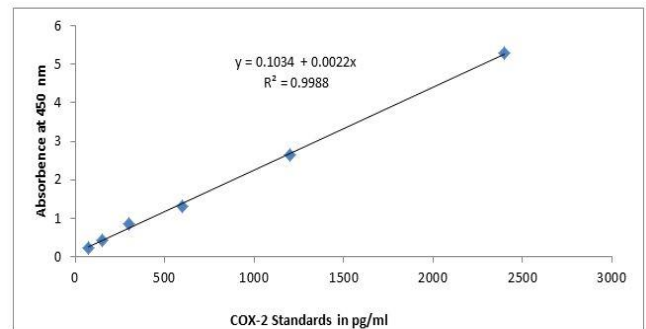


Fig. 1: Standards curve of COX-2 in pg/ml

Detection of the concentration of nimesulide and aspirin in plasma by using HPLC

Nimesulide was injected in the first group of mice at 15.8 mg/kg, i.m., whereas the second group of mice was treated with aspirin at 424.5 mg/kg, i.m. The blood was gained from the two groups of nimesulide and aspirin at five times: 0.5, 1, 2, 4, and 24 h (each time consisted of 5 mice for each drug). The plasma was then obtained by centrifugation (4000 rpm for 15 minutes, Chalice, UK) into EDTA tubes as an anticoagulant after incubation (at room temperature for 10–20 minutes). The samples were preserved (-18 °C) until assessment by using high-performance liquid chromatography (HPLC) (Shimadzu, Japan) with ultra-

violet detection (Kim *et al.*, 2012; Guillé *et al.*, 2019; Ramesh *et al.*, 2019).

Preparing the different standards of nimesulide and aspirin

The nimesulide standards were made as 10, 20, 40, 80, 160, and 320 µg/ml concentrations by diluting the mobile phase composed of triethylamine (0.2%) : methanol at 1:1 volume/volume and (pH = 3) tuned using phosphoric acid. The net solution was then filtered (0.45 µm filter paper) (Millipore, England) and then underwent degassing (Prinesh *et al.*, 2000; Ptáček *et al.*, 2001). Lastly, the net solution was injected into the HPLC apparatus (20 µl) and examined at a wavelength of 300 nm by using HPLC with a flow rate of 1.5 ml/min and a run time fixed for 10 min. while aspirin standards were made of 25, 50, 100, 200, 400, and 800 µg/ml concentrations by using the mobile phase containing acetonitrile and water at 35:65 volume/volume. The solution was filtered and degassed. The wavelength used for aspirin assessment was 238 nm. The flow rate was set to 1.5 ml/min, and a run time was fixed for 10 min (Rubak *et al.*, 2013; Cheng *et al.*, 2022).

Equation (y=a+bx) was the simple linear regression estimated from the nimesulide (R²=0.9838) and aspirin (R²=0.9994) standards, used for the calculation of individual nimesulide and aspirin concentrations in the plasma for both groups (Figs. 2 and 3), where ‘y’ represent the peak of area for the plasma samples identified at 300 nm for nimesulide and 238 nm for aspirin by the HPLC, ‘a’ was the intercept for nimesulide (143080) and for aspirin (841386), ‘b’ was the slope nimesulide (15393) and aspirin (166368), and ‘x’ represent the nimesulide and aspirin concentration of unknown plasma samples.

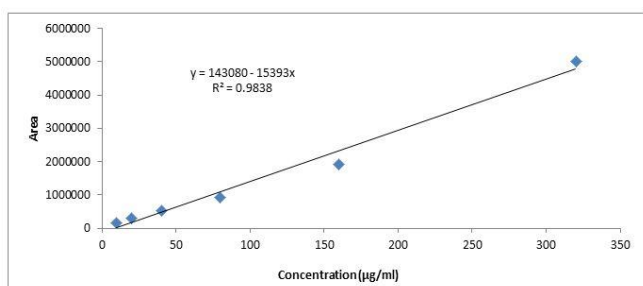


Fig. 2: Nimesulide standards curve in µg/ml

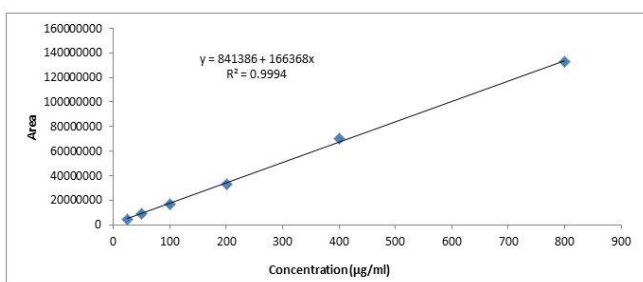


Fig. 3: Aspirin standards curve in µg/ml.

Liquid-liquid extraction (LLE)

The method of LLE was used, which was an accurate, simple, and approved procedure for nimesulide and aspirin, which are useful for precipitating proteins in the plasma (Ravi *et al.*, 2017; Kim *et al.*, 2022). The method is composed of the addition of acetonitrile to the plasma at 1:1 v/v. After that, the mixture was vortexed for up to 5 minutes for nimesulide and 1 minute for aspirin and centrifuged (at 3500 rpm for 15 min.). The supernatant was then subjected to filtration and degassing (0.45 µm filter paper). Finally, the sample was injected (20 µl) into the apparatus and examined by HPLC at 300 and 238 nm, respectively.

Measuring nimesulide and aspirin pharmacokinetic variables

A model of non-compartment was used to obtain the pharmacokinetic parameters for the two groups mentioned above by a PKSolver program plug-in Excel (Zhang *et al.*, 2010). The parameters of pharmacokinetics involved area under moment curve (AUMC_{0-∞}) (µg.h²/ml), area under curve (AUC_{0-∞}) (µg.h/ml), elimination rate constant (K_{el}) (0.693/t_{1/2β}) (h⁻¹), maximum concentration (C_{max}) (µg), half-life (t_{1/2β}) (h), mean residence time (MRT) (AUMC/AUC)(h), maximum time (T_{max}) (h), clearance (Cl) (dose/AUC) (L/h/kg), and volume of distribution (V_{ss}) [dose × AUMC/(AUC)²] (L/kg).

Statistical analysis

One-way analysis was the statistical examination of parametric data which was achieved through the comparison of multiple means. The unpaired student T-test was used to analyze the means of the two groups of mice (Berke, 2007). The significance was at the probability P<0.05.

RESULTS

ED_{50s} of nimesulide and aspirin in mice

The estimated ED_{50s} value of nimesulide and aspirin were 7.9 and 212.23 mg/kg, i.m., respectively which reveals the dose that injected i.m. resulted in an analgesic (therapeutic) effect in 50% of the mice in the trial (Table 1).

Table 1: The analgesic ED_{50s} of nimesulide and aspirin in mice

Parameters	Nimesulide	Aspirin
ED ₅₀ = xf + (k × d)	7.9 mg/kg, i.m.	212.23 mg/kg, i.m.
Initial dosage	10 mg/kg	100 mg/kg
Last dosage (xf)	10 mg/kg	190 mg/kg
Table (k) value	-0.701	0.741
± Doses (d)	3 mg/kg	30 mg/kg
Dosages used	10-7 mg/kg	100-220 mg/kg
No. of mice	5 (XOXOX)	8 (OOOOXOXO)

X directed to analgesia while O designated as no analgesia

Comparative inhibition of COX-2 concentration between nimesulide and aspirin in plasma, liver, and kidney of mice

The concentration of COX-2 in plasma of the negative control group was 753.59 pg/ml, while the nimesulide and aspirin-treated groups (at 15.8 and 424.5 mg/kg, i.m., respectively) decreased the COX-2 concentration to 680.44 and 688.43 pg/ml, respectively. The COX-2 concentration in the positive control group (1% acetic acid-AA) was 772.796 pg/ml, while the group injected with nimesulide after 30 minutes of AA injection was significantly decreased to 588.59 pg/ml and the group of aspirin to 594.43 pg/ml. The COX-2 concentration of the liver in the control group was 954.12 pg/ml; the nimesulide and aspirin-treated groups reduced the enzyme activity to 922.06

and 931.10 pg/ml, respectively. The positive control group was 980.23 pg/ml, while treated groups with nimesulide+AA and aspirin+AA decreased the concentration of COX-2 to 905.05 and 924.57 pg/ml, respectively.

The COX-2 concentration of the kidney in the negative control group was 1028.22 pg/ml; the treated group with nimesulide and aspirin decreased to 926.32 and 926.31 pg/ml, respectively. The positive control was an increase in the concentration of COX-2 to 1039.01 pg/ml, while treated groups nimesulide+AA and aspirin+AA decreased in the concentration of COX-2 significantly (**Table 2**).

Table 2: COX-2 concentration in mice: The inhibition by nimesulide and aspirin administration

Groups	COX-2 concentration (pg/ml)		
	Plasma	Liver	Kidney
Non-inducible Mice (NS)			
Negative control Normal saline (NS)	753.59 ± 88.01	954.12 ± 80.30	1028.22 ± 5058
Nimesulide+ NS	680.44 ± 68.88	922.06 ± 33.28	926.32 ± 92.15
Aspirin+ NS	688.43 ± 80.71	931.10 ± 56.71	926.31 ± 59.85
Inducible Mice (AA)			
Positive control- Acetic acid (AA)	772.80 ± 75.81	980.23 ± 48.77	1039.01 ± 43.18
Nimesulide+AA	588.59 ± 43.85*	905.05 ± 39.04	902.37 ± 39.94*
Aspirin+AA	594.43 ± 55.93	924.57 ± 40.73	917.81 ± 38.97*

Numbers represented in the table as mean ± Standard Error (5 mice/group).

* Significantly difference in contrast to the positive control group at $P < 0.05$.

Detected the concentration of nimesulide and aspirin in plasma by HPLC

Measuring the nimesulide plasma concentrations at 0.25, 0.5, 1,2,4, and 24 hrs were 14.62, 9.22, 9.88, 7.38 and 2.27 µg/ml, respectively while the concentrations of aspirin were 4.35, 3.17, 2.54, 2.25 & 1.21 µg/ml, respectively (**Table 3 Fig. 4**).

Table 3: The concentration of individual nimesulide and aspirin in plasma (µg/ml) at multiple times measured.

Time (Hour)	Groups	
	Nimesulide	Aspirin
0.5	14.62±2.60	4.35±0.72*
1	9.22±0.91 ^a	3.17±0.19*
2	9.88±0.25 ^a	2.54±0.22*
4	7.38±1.43 ^a	2.25±0.25 ^{*,a}
24	2.27±0.48 ^{a,b,c,d}	1.21±0.23 ^{a,b,c}

* Differs significantly in contrast to the nimesulide group ($P < 0.05$).

^a Differs significant from 0.5 h in the same group ($P < 0.05$).

^b Differs significant from 1 h in the same group ($P < 0.05$).

^c Differs significant from 2 h in the same group ($P < 0.05$).

^d Differs significant from 4 h in the same group ($P < 0.05$).

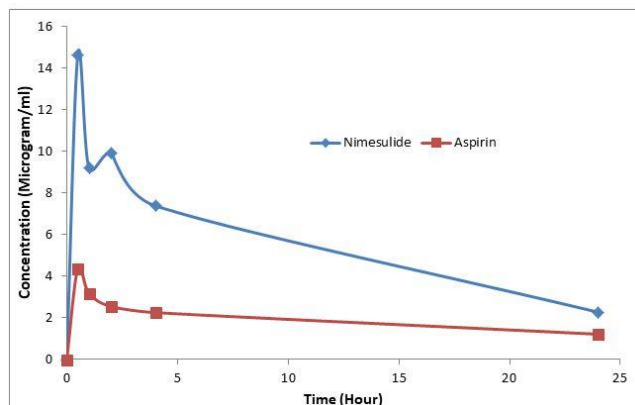


Fig. 4: Comparative concentrations of nimesulide and aspirin in plasma of mice.

Pharmacokinetic variables of nimesulide and aspirin in mice

Nimesulide pharmacokinetic variables were (AUC_{0-∞} 169.18, AUMC_{0-∞} 2358.72, K_{el} 0.06, C_{max} 14.62, T_{max} 0.5, t_{1/2β} 11.07, MRT 13.94, V_{ss} 1.49, and Cl 0.09) while aspirin pharmacokinetic parameters were (AUC 82.31, AUMC 2428.32, K_{CL} 0.03, C_{max} 4.35, T_{max} 0.5, t_{1/2β} 21.25, V_{ss} 158.12, Cl 5.16) (Table 4).

Table 4: The pharmacokinetic variables of nimesulide and aspirin in mice

Variables	Groups	
	Nimesulide	Aspirin
AUC _{0-∞} (µg ×h /ml)	169.18	82.31
AUMC _{0-∞} (µg ×h ² /ml)	2358.72	2428.32
MRT (h)	13.94	29.50
t _{1/2β} (h)	11.07	21.25
Tmax (h)	0.5	0.5
Cmax (µg)	14.62	4.35
KeI (h ⁻¹)	0.06	0.03
V _{ss} (L /kg)	1.49	158.12
Cl (L /h /kg)	0.09	5.16

Nimesulide was injected at 15.8 mg/kg, i.m. and aspirin at 424.5 mg/kg, i.m.

Variables is a model of non-compartment pharmacokinetic measurement.

PKSolver program used for assessment of pharmacokinetics.

DISCUSSION

In this research, we focus on the inhibitory action of selective (nimesulide) and non-selective (aspirin) against COX-2 and their comparison at the level of analgesia (pharmacodynamics), besides their pharmacokinetics in mice. Nimesulide and aspirin were considered NSAID drugs that have numerous therapeutic effects in human and veterinary fields because of their different medical effects as antipyretic, anti-inflammatory and analgesic drugs (Balaji *et al.*, 2013). The effects occur due to a reduction of the COX-2 enzyme, which inhibits prostaglandin E₂ biosynthesis (Hemmateenejad *et al.*, 2008). The analgesic effect, represented by ED_{50s}, of nimesulide and aspirin was studied in previous research in humans (Pong *et al.*, 1985), mice (Gupta *et al.*, 2000) and dogs (Guillé *et al.*, 2019).

The data show that nimesulide has a better analgesic effect at a small dose of 7.9 mg/kg (ED₅₀), while 212.23 mg/kg of aspirin is needed to cause analgesia in half of the animal population. So, nimesulide and aspirin have different profiles of action on COX-2 when the drugs were given as a single injected dose (represented as ED₁₀₀) to treat the pain and inflammation (induced by acetic acid-AA), which led to a significant lowering of the COX-2 level in the

plasma and kidneys of a group treated with AA after 30 minutes of nimesulide injection, whereas the level of COX-2 decreased significantly in the kidneys of a group treated with AA after 30 minutes of aspirin injection, which means that nimesulide acted as a selective COX-2 inhibitor more than the drug acted as a non-selective COX-2 (aspirin).

At the level of drug concentration in the plasma, which was measured by HPLC in this study, we found that the concentration maximum (C_{max}) as well as the AUC of nimesulide were higher than aspirin at 0.5, 1, 2, 4, and 24 h times. These results were in accordance with similar previous research in humans (Pong *et al.*, 1985) and mice (Gupta *et al.*, 2000), as well as the other parameters findings of nimesulide and aspirin such as T_{max}, t_{1/2β}, and CL, which are in accordance with previous studies (David *et al.*, 2013). This may be attributed to the fact that nimesulide metabolites called 4-amino-2-phenoxy-methanesulfonanilide (M1) have an active constituent biologically. A recent study validated that M1 is a metabolite with susceptibility to oxidation by cytochrome enzymes (P₄₅₀) that produce a reactive intermediate (M2). The development of the intermediate chemical compound occurs due to specific P₄₅₀ enzymes (2C19 and 1A2) by way of the two principals of P₄₅₀ enzymes. M1 breakdown was irreversibly reduced by 2C19, but 1A2 triggered it in a time-dependent paradigm. Exclusively, 2C19 facilitated the additional metabolism of M1 to aminohydroxynimesulide (M3) and to diiminoquinone (M4).

Another reason was the protein binding of nimesulide, which was 97.5% (Li *et al.*, 2009), while aspirin protein binding was 81.7% (Palikhe *et al.*, 2011), so the volume of distribution of nimesulide was 1.49 L/kg smaller than that of aspirin (158.12 L/kg), so the concentration of nimesulide was greater than the concentration of aspirin in plasma, as revealed in this study. The metabolism of aspirin by UDP-glucuronosyltransferase (UGT), cytochrome 2C9 (CYP2C9), and N-acetyl transferase 2 (NAT2) produces slow metabolizing enzymes (Palikhe *et al.*, 2011); this interpretation may be the reason for the longer half-life of aspirin (21.25 h) in comparison to nimesulide (11.07 h). All the above-mentioned reasons rely on nimesulide efficacy at the pharmacodynamic level, which produces efficient pharmacological properties.

CONCLUSION

The study concluded that nimesulide has superior pharmacological properties (analgesic, antipyretic and anti-inflammatory) than aspirin due to its ability to inhibit COX-2 more selectively and its unique pharmacokinetics in mice, which may be useful in veterinary medicine.

Conflicts of interest

All authors declare that they have no conflict of interest.

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