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Review

# Is acetylsalicylic acid use in cats contraindicated or limited indicated?

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**Abstract:** Acetylsalic acid, (Aspirin®) is a non-steroidal anti-inflammatory drug (NSAID) widely used in human and veterinary medicine, especially for its analgesic and antithrombotic effects, mainly in the prevention of cardiovascular complications and in the treatment of various diseases. Aspirin® can not be metabolized in cats because they do not have the enzyme glucuronyl transferase. For this reason, it has a long half-life and a narrow dose range. High dose administration in cats may cause serious toxicity in the liver. Acetylsalicylic acid is known to cause gastric ulcers associated with decreased prostaglandin levels. For these reasons, it is considered toxic to cats. But it also has antipyretic, analgesic, anti-inflammatory and antithrombotic properties. It is indicated for use alone or in combination with other antithrombotic drugs in the treatment and prophylaxis of thrombus formation resulting from cardiovascular diseases. This review aims to examine the indicated and contraindicated areas of use of Aspirin®, which is widely considered toxic in cats.

**Keywords:** aspirin; NSAID's; ulcer; salicylate; thromboembolism; toxicity

## 1. Introduction

Acetylsalicylic also known as Aspirin®, is widely used in human and veterinary medicine [1]. Aspirin® was initially used only for its analgesic effects, but over time its antipyretic, anti-inflammatory and antithrombotic effects were also discovered. Today, its use in human medicine is quite common, but its use in cats is controversial [2].

Aspirin® has been widely thought to be toxic in cats for years, as reported in many studies, but studies are being conducted to examine whether it can be used in low doses due to its anti-inflammatory and antithrombotic effects in patients with pain, fever, and cardiovascular diseases. Its effectiveness has been reported and suggested to be indicated, especially in cardiovascular diseases and the prevention of arterial thromboembolism [3]. It is also claimed that the use of Aspirin® prolongs life in geriatric patients because it reduces the risk of various diseases [4]. However, cats are more sensitive to Aspirin® than humans and dogs [5]. The half-life of Aspirin® is longer in cats than in other animals (especially dogs) [6]. The reason for this is thought to be the slowness of glucuronidation [7].

As a result of the combination of a toxic substance with glucuronic acid, it transforms that drug into a form that is less toxic than original substance, more water soluble and more easily excreted from the body. This physiological situation is called glucuronidation. However, glucuronidation in the cat body is very slow than other animals and incomplete. For this reason, the elimination of Aspirin® from the cat body is very slow. This increases the half-life of Aspirin® in the cat body [8]. On the other hand, it is thought that one of the reasons for the slow clearance of Aspirin® from the

body may be due to the weak glycine conjugation. However, it has many side effects in cats and, at higher doses, in humans or dogs [9].

It has been mentioned in numerous literature over the years that Aspirin® causes gastric hyperemia and ulceration in dogs and rabbits. In the years following its discovery, similar situations were observed with intravenously administered Aspirin®. This has shown that Aspirin® can damage the gastric epithelium even if it does not come into contact with the stomach mucosa [10]. For this reason, studies were carried out to produce a drug that has as many indications and effects as Aspirin®, but has fewer side effects on the gastrointestinal tract. As a result of these studies, the active ingredient ibuprofen was discovered in 1961 [2]. Despite the toxicity of Aspirin®, especially in cats, Aspirin® is still considered indicated in some diseases today, even if different medications are used. Therefore, in this review study, a perspective on limited indications versus contraindications is examined.

## 2. History of aspirin

Aspirin® is one of the most widely used drugs today. It has been the most interesting drug throughout history. Its history dates back to 3500 years ago. It was used by Sumerians and Egyptians for joint diseases. During these periods, it was obtained as extracts from the willow tree (especially its bark) and these extracts were applied topically [11]. Later, it was recorded that it was used during the times of Hippocrates and Galen, the famous scientists of the period, and it was used for analgesic purposes in a geography extending from South Africa to North America [12]. It is mentioned that it is used especially for joint pains and headaches during these periods. Later, in the third century, the use and effect of salicylates spread to the Far East [11].

In the 18th century, the willow tree was mentioned as “The Bark of an English Tree” by Lord Edward Stone. Lord mentioned its analgesic properties and suggested its use in the treatment of malaria [13]. In the following century, it was studied for its commercial form and its extract was obtained and put on the market [14]. The commercial form of acetylsalicylic acid spread throughout the world soon after it was produced and became widespread immediately. It was used by famous people during these periods. State leaders were also among these people. Even famous writers mentioned Aspirin® in their books and works. This fame made the drug itself the subject of textbooks. As the years progressed, it began to be produced in different ways by different manufacturers. However, information about the mechanism of action was very limited [11].

In the 1900s, Aspirin® and other NSAIDs began to be investigated in more detail, and a number of studies were conducted only in the later years of the 20th century [11]. In these studies, prostaglandins were studied for their mechanism of action. One of the most important of these was made by Sir John Robert Vane. The study was published in 1971 and focused on the mechanisms of action of aspirin-like drugs. The study mentioned, but was not limited to, the antipyretic, anti-inflammatory and analgesic effects of anti-inflammatory drugs. In addition, its bronchoconstrictor effects were also mentioned. In addition to the mechanism of action, gastrointestinal effects were mentioned as side effects. In this regard, peptic ulcers have been mentioned [15]. This

study shed great light on the unknown mechanism of action of Aspirin® [11]. Despite such side effects, different drugs such as ibuprofen have also been discovered [2].

In the following years, the mechanism of action of Aspirin® became much clear and its antithrombotic effects began to be mentioned. This situation has set an important example for the uses of Aspirin® other than its anti-inflammatory properties. It has been shown that it can be used and even indicated in the treatment of cardiovascular diseases [11].

Today, it is known that Aspirin® is indicated for the treatment of many diseases and also has many side effects. Studies are progressing further than the mechanism of action, towards indication areas and reducing side effects. For this purpose, the aim is to determine appropriate dose ranges, determine the lowest effective dose ranges throughout the disease and use them correctly. Studies are being conducted on the use of Aspirin® in many areas beyond anti-inflammatory processes, from cardiovascular diseases to cancer treatment. In modern days, it is known as the most widely used drug in the world [11].

## 3. Mechanism of action

Although Aspirin® is a weaker analgesic than strong analgesics, it is a very effective analgesic for mild and moderate pain [4]. It is an ester of acetic acid hydrolyzed to salicylic acid by esterases found in the gastrointestinal tract and liver and is a weak acid [2].

Aspirin® is absorbed from the stomach and duodenum because it is lipophilic [12]. The absorption of the drug depends on many factors such as stomach pH and food intake [16]. It inhibits the biosynthesis of thromboxane A2 (TXA2) and other prostaglandins. TXA2 is a prostanoid produced by the oxidation of arachidonic acid produced from membrane phospholipids. Arachidonic acid, on the other hand, plays a role in the production of prostaglandin H2 (PGH2) and TXA2 through its cyclooxygenase (COX) activity [14]. They permanently inhibit COX function. Finally, they are cleared from the body by conjugation with glucuronic acid and glycine [17]. They are excreted from the body through the kidneys, and the excretion rate may vary depending on the urine pH [16]. As the urine pH increases, their excretion from the urine increases, and while they are excreted from the urine, they also reduce the pH of the urine [18].

Aspirin® is a phenol compound and it can not be adequately glucuronidated in cats due to glucuronyl transferase deficiency. However, dogs may tolerate Aspirin® better [2]. It is also suitable for use in cattle and goats. They are not preferred in newborns because biotransformation is insufficient and urinary excretion is limited. The absorption of enteric-coated Aspirin® is thought to be low [18].

## 4. Contraindications

Aspirin® may increase bleeding times and lead to anemia due to its antiplatelet effect [19]. Additionally, it should be used with caution in patients with respiratory diseases as it may cause oxidative damage and asthma [20]. Aspirin® causes blood pH to increase due to hyperventilation and associated $CO_2$ loss. This may result in

respiratory alkalosis. The kidneys may cause metabolic acidosis by secreting bases such as sodium bicarbonate to reduce the increasing pH. Aspirin® causes blood pH to increase due to hyperventilation and associated $CO_2$ loss. This may result in respiratory alkalosis. The kidneys may cause metabolic acidosis by secreting bases such as sodium bicarbonate to reduce the increasing pH [19]. In addition, due to its undesirable effects such as gastrointestinal ulcers, its therapeutic index is very narrow and therefore it should be used with extreme caution. Compared to Aspirin®, the use of clopridogrel, which has fewer side effects in terms of its antithrombotic effect, is preferred. However, its combined use with Aspirin® has been reported to cause gastrointestinal side effects in humans [6].

Aspirin® can cause serious toxicities in the liver of cats [21]. Almost all NSAIDs can cause stomach damage. Most NSAIDs are acidic and damage the gastric mucosa. NSAIDs may reduce mucosal proliferation. However, whether mucosal proliferation can cause gastropathy is still a matter of debate. In particular, the local toxic properties of Aspirin® are known. Aspirin® causes fever, respiratory alkalosis, metabolic acidosis, stomach irritation and liver necrosis. Ataxia and seizures may occur at high doses. Additionally, electrolyte disorders and depression may occur [17]. At the same time, Aspirin® is assumed to be a hemolytic agent and may cause hypoprothrombinemia [21]. In human studies, it has been reported that Aspirin® may cause acute renal failure [22]. It can cause deterioration of kidney function in people with chronic kidney disease (CKD). CKD, the most common kidney disease in cats, is especially common in older cats and is irreversible. As a result of the disease, there is a decrease in kidney functions. Since it is a progressive disease, the aim is to slow the progression of the disease. The disease may also cause thrombosis. For this reason, its use is not recommended, especially in geriatric patients and patients with CKD [6]. Also NSAIDs can cause severe organ damage [16].

The reason why it causes stomach ulcers is thought to be related to the decrease in mucosal prostaglandin levels due to inactivation of the prostaglandin system [23]. It is thought that a barrier disorder occurs in the back diffusion of hydrogen ions of Aspirin®, which is absorbed through nonionic diffusion. As a result, lesions and injuries may occur due to the back diffusion of hydrogen ions into the mucosa. However, these hypotheses can not explain the gastric lesions formed in Aspirin® applications outside the gastrointestinal tract [24].

Aspirin® reduces prostaglandin formation and increases leukotriene formation, which has inflammatory effects. This makes the stomach non-resistant to simple ulcerogenic agents. It is also deacetylated with salicylate immediately after inhibition of COX activity. Aspirin® and salicylate are toxic to mucosal epithelial cells. Salicylate disrupts mucosal barrier function, reduces ATP and accelerates proton loss [20]. Aspirin® can also cause mucosal damage in the intestine [25].

Especially its use with corticosteroids or other NSAIDs increases the risk of stomach ulcers. For this reason, it should not be used with other NSAIDs [16]. Renal excretion may be delayed with some drugs, such as furosemide. In addition, drug effectiveness decreases when used together with Furosemide in heart diseases. It has been reported that it reduces or prevents the effectiveness of spironolactone [18].

In a study conducted in the past years, it was reported that intravenous Aspirin® administration alone did not cause stomach ulcers, but its combined use with histamine

caused stomach ulcers [26]. In a similar study, it was reported that intravenous histamine and intravenous Aspirin® caused stomach ulcers equally in cats [27]. Additionally, the risk of erosion increases if there is ongoing bleeding in the stomach [28]. For this reason, it is recommended to take Aspirin® with or after a meal on a full stomach and use it together with stomach protectors such as proton pump inhibitors or H2-receptor antagonists [25].

It has been suggested that Aspirin® may cause hypoplasia in the bone marrow. In a study, severe anemia and Heinz bodies in red blood cells were observed in some cats treated with Aspirin®, and the cause of the anemia was thought to be due to gastrointestinal tract bleeding [21]. It is unsafe to use in pregnant animals and has teratogenic effects. It can also delay birth. In addition, there is a risk of bleeding in long-term use, it can pass through the placenta and decrease to fetal levels and even pass into milk [18].

NSAIDs should not be used in cats with sensitivity, anemia, stomach ulcers, asthma, and organ failure such as the liver, as they are eliminated from the body as a result of liver metabolism. In addition, it should be used with extreme caution in creatures that are dehydrated or have other abnormal clinical findings [16].

Gastric lavage, symptomatic and supportive treatment are applied for treatment of toxicity [17]. In fact, some veterinarians do not recommend prescribing Aspirin® to cats, even in low doses [21]. It should be used with caution, especially in elderly cats and cats with kidney or liver disease [12]. In addition, although its use in the treatment of pain, fever and inflammation is not clear enough, reports of toxicosis due to Aspirin® are very few [17,18].

## 5. Indications

NSAIDs are used specifically to treat inflammation. The concept of inflammation is the reaction of the tissue due to damage. This may be caused by microorganisms such as bacteria and viruses, but also by physical factors such as heat or trauma. In such cases, the analgesic properties of aspirin are used. However, aspirin prevents the body temperature from rising as a result of the inflamed area, due to its antipyretic properties [16]. It is recommended to use it in combination with opioids for pain management in cats. At the same time, its anti-inflammatory effect is used in the treatment of arthritis. The many therapeutic effects of aspirin are very advantageous for veterinary medicine [16].

It has been reported that the increase in body temperature caused by bacterial pyrogen was reduced from 40.2 ℃ to 39.30 ℃ with Aspirin® and the prostoglandin-like activity in the cerebrospinal fluid was reduced [29]. Pain management is a big problem in cats. Because cats are extremely sensitive to most drugs and most drugs are toxic to cats. However, Aspirin® can be used for short periods of time [30]. Its analgesic, anti-inflammatory and antithrombotic effective dose is administered enterally every 48–72 h [18].

Nowadays, its use in cats has become widespread, especially due to its antithrombotic effect [17]. It can be used in the treatment and even prevention of thrombosis that occurs as a result of heart and brain diseases [25]. It is also recommended to prevent thrombosis in diseases such as cardiomyopathy and

heartworm [17]. By inhibiting the COX enzyme, NSAIDs suppress the production of TXA2, which is the activator of platelet aggregation [1].

Thromboembolism may occur as a result of cardiac, inflammatory, metabolic or neoplastic processes [31]. While in the systemic circulation, thrombi can occlude arterial segments and alter tissue perfusion. Treatment options are limited and relapses are common [32]. Aspirin® permanently inhibits the COX activities of PGH synthase-1 and PGH synthase-2 [31]. There are three different cyclooxygenase enzymes: COX-1, COX-2 and COX-3. While COX-1 plays a role in cell communication, COX-2 plays a role in the production of prostanoids responsible for inflammatory reactions in inflamed areas. As a result of acetylsalicylic acid inhibiting COX-2, analgesic and anti-inflammatory effects are observed. COX-3 plays a role in pain and increase in body temperature, especially in humans [16]. COX-1 and COX-2 catalyze the conversion of arachidonic acid to PGH2, the precursor of TXA2. TXA2 induces platelet aggregation and vasoconstriction. As a result, platelet function increases. Vascular endothelial cells convert PGH2 into prostacyclin (PGI2). PGI2 inhibits platelet aggregation and induces vasodilation. TXA2 is produced by platelets via COX-1. PGI2 is produced by the vascular system with COX-1 and COX-2. Aspirin® also creates permanent defects in TXA2 synthesis (**Figure 1**) [31].

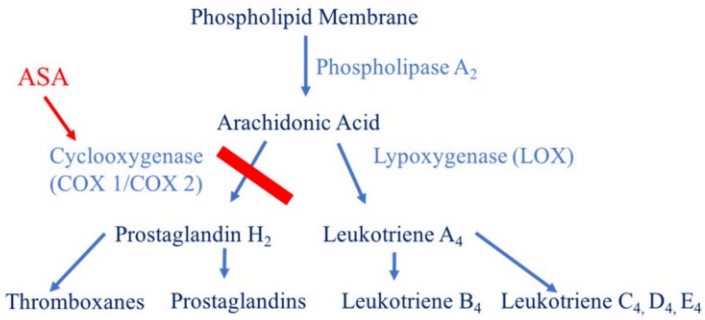


**Figure 1.** As a result of the binding of acetylsalicylic acid to COX-1 and COX-2, it causes the inhibition of protsaglandins and, as a result, platelet aggregation. ASA: Acetylsalicylic asid [33].

Hypertrophic cardiomyopathy is the most common disease that causes heart failure in cats. While the disease fundamentally changes the functioning of the heart, it also changes the level of trace elements. While copper levels are high in male cats, a study on canine dilated cardiomyopathy showed significant changes in selenium levels depending on age [34,35]. It has been suggested that platelets may be hyperreactive in cats with hypertrophic cardiomyopathy (HCM). On the other hand, it is suggested that although Aspirin® can not completely prevent platelet aggregation, it may limit it to some extent [1]. Aortic thromboembolism may develop in cats with HCM. The most important factors in this risk factor are left atrial enlargement and associated weakness of function. For this reason, the use of clopidogrel is recommended in cats with HCM and at risk of developing aortic thromboembolism. Clopidogrel is constantly spit out by cats due to its bad taste and also does not completely eliminate the risk of aortic thromboembolism. For this reason, it is recommended to use it in combination with another antithrombotic drug, especially

aspirin [36]. Aspirin® may be considered as a treatment option in cats with left atrial enlargement. For this purpose, it is aimed to reduce platelet function [37]. However, Aspirin® can not be used alone as an antithrombotic agent in cats with cardiomyopathy [38]. It has been reported that the combination of clopidogrel and Aspirin® may be effective in the treatment of arterial thromboembolism [39]. Additionally, there are opinions arguing that clopidogrel is much more effective and better tolerated than Aspirin® [32]. Platelet levels are important in determining the risk of thrombus in cats with HCM. The decrease in platelet count increases the number of platelets and a hypercoagulative state occurs. Although the use of acetylsalicylic acid appears to be indicated in cats at risk of thrombus, further studies are recommended to evaluate the risk of thrombus in cats with HCM, particularly based on blood parameters such as platelets [40].

In some studies, it has been reported that Aspirin® increases the survival rate after endotoxin applications [41]. Other studies have also reported that Aspirin® inhibits acute vascular responses to endotoxins in cats [42]. In human cancer studies, the anti-cancer activity of Aspirin® has been suggested. Accordingly, it is thought that Aspirin®'s antithrombotic and anti-inflammatory effects may prevent cancer [43]. However, the platelet inhibition effectiveness of Aspirin® is still a matter of debate [37]. Aspirin also has pro-apoptotic effects. It destroys cancer stem cells and also inhibits the genes that cause cancer development. In this regard, it induces the arrest of G0/G1 cell cycle phases [44].

Clarence et al. (1990) examined the effect of Aspirin® in cats experimentally transplanted with heartworms, but no satisfactory response was obtained. However, as a result of the study, less arteriosclerosis was observed [45]. According to some studies, Aspirin® increases the absorption of ascorbic acid from the intestines, while other studies have observed that its excretion in the urine increases [46]. It has also been reported to suppress the development of lung lesions [41].

Aspirin® is recommended at a dose of 10–20 mg/kg twice a day for dogs and once every other day for cats. Toxicosis may not be observed in cats at doses of 25 mg/kg every other day [6]. In a study conducted on this subject, a clinical improvement of nearly 50% was reported with the use of Aspirin® at a dose of 25 mg/kg every three days in cats with thromboembolism [47]. The clinical efficacy of lower doses is still a matter of debate [6].

In one study, 35 cats received Aspirin® at doses ranging from low doses up to 200mg/kg, resulting in mucosal lesions, including ulcers. However, the frequency of lesions did not change in cats given low doses. Additionally, as a result of applications at a dose of 200 mg/kg, a decrease in body weight, anorexia and even death was observed. In the same study, death was observed even at relatively lower doses of 50mg/kg, and bronchopneumonia was found on necropsy [24].

## 6. Safer use of acetylsalicylic acid

Although acetylsalicylic acid is widely used in human and veterinary medicine, it has many side effects. The most discussed side effect in the literature is gastrointestinal mucosal damage. This carries the risk of damaging the gastric mucosa even at very low doses in cats and humans. For this reason, its administration to those

at risk of bleeding, those who have previously had a stomach ulcer, and geriatric patients is limited [44]. Despite all this, there are many indications in both human and veterinary medicine. Therefore, using aspirin in safer doses or the production of a safer Aspirin® model is of great importance for human and veterinary medicine. Studies on this subject are not yet sufficient.

Despite the side effects of Aspirin®, various studies have been conducted, especially in human medicine. These studies were generally conducted for gastrointestinal effects. For this reason, instead of bolus administration, low-dose infusion applications were tried and as a result, a high degree of platelet selectivity was obtained. However, it has the potential to cause inflammation in the gastrointestinal tract. It has also been suggested that Aspirin® is absorbed through the skin as a result of transdermal applications and may reduce gastrointestinal side effects [48]. In addition, simultaneous use with proton pump inhibitors or H2 receptor antagonists is recommended [44].

A method developed against gastrointestinal side effects is the use of enteric-coated Aspirin tablets. It is thought that this type of Aspirin® tablets may cause less damage to the gastrointestinal mucosa. It has also been suggested that enteric-coated tablets will cause less erosion in long-term use [14]. It has also been reported that the cardiovascular prophylactic effect of enteric-coated Aspirin tablets remains sufficient [49]. However, TXA2 inhibition of enteric-coated Aspirin tablets is much lower than standard Aspirin tablets. Moreover, although it does not damage the gastric mucosa, it may cause mucosal erosion in the small intestine. This brings into focus the discussion that enteric-coated tablets have clinically significant improvements [50].

In one study, the prostaglandin analog misoprostol, which is used to prevent gastrointestinal lesions resulting from the use of NSAIDs in humans, was tested on dogs. It has been suggested that misoprostol inhibition of stomach acid production may be effective against the gastrointestinal side effects of NSAIDs. As a result, it has been reported that if misoprostol is given to dogs treated with aspirin, it can prevent the development of gastroduodenal lesions [51].

As a result, methods to reduce the gastrointestinal side effects of Aspirin include avoiding long-term use and simultaneous use of other anticoagulants or steroidal drugs. In addition to medications, the use of NSAIDs with alcohol or in the presence of bacterial infection increases the risk of gastrointestinal, mucosal damage and even bleeding. It is recommended to use it together with stomach protectors such as proton pump inhibitors or H2-antagonists [52]. Despite the negative effects of aspirin-induced COX inhibition, prostaglandin-inducing agents can be used or external prostaglandin application can be made [44]. Apart from these, the mechanisms associated with a safer form of aspirin are still under investigation. Discovery of these forms or mechanisms will be a ray of hope for many future treatments, especially in cats.

## 7. Conclusions

Acetylsalicylic acid is a non-steroidal anti-inflammatory drug used in a wide range of areas, from simple pain management to the treatment of complex cardiovascular complications. While it has a wide range of uses, especially in human medicine, its use is limited in cat practice because it can not be glucuronidated

sufficiently. It is especially known to cause stomach ulcers. However, despite its contraindications, there are many indication areas in cats. It is possible to benefit from its antithrombotic effects in inflammatory and heart diseases. However, it should be used with caution due to its side effects. The effectiveness of aspirin needs to be studied further. We believe that if studies are carried out to reduce the toxic effects of the drug in cats, it will find use in the treatment of many diseases with correct dosing and use in the right situations.

**Conflict of interest:** The authors declare no conflict of interest.

## References


1. Cathcart CJ, Brainard BM, Reynolds LR, et al. Lack of inhibitory effect of acetylsalicylic acid and meloxicam on whole blood platelet aggregation in cats. Journal of Veterinary Emergency and Critical Care 2011; 22(1): 99-106. https://doi.org/10.1111/j.1476-4431.2011.00681.x.
2. Khan SA, McLean MK. Toxicology of frequently encountered nonsteroidal anti-inflammatory drugs in dogs and cats. Veterinary Clinics of North America Small Animal Practice 2012; 42(2): 289-306. https://doi.org/10.1016/j.cvsm.2012.01.003.
3. Fuentes VL, Abbott J, Chetboul V, et al. ACVIM consensus statement guidelines for the classification, diagnosis, and management of cardiomyopathies in cats. Journal of veterinary internal medicine 2020; 34(3): 1062-1077. https://doi.org/10.1111/jvim.15745.
4. Vane JR and Botting RM. The mechanism of action of aspirin. Thrombosis research 2003; 110(5-6): 255-258. https://doi.org/10.1016/s0049-3848(03)00379-7.
5. Albo AG, Nebbia C. Incidence of Poisonings in Domestic Carnivores in Italy. LVII Annual Meeting of the Italian Society for Veterin Ary Sciences (SISVET); 2003 Ischia; Veterinary Research Communications; 2004. p.83-88.
6. De Santis F, Boari A, Dondi F, et al. Drug-Dosing Adjustment in Dogs and Cats with Chronic Kidney Disease. Animals 2022; 12(3): 1-29. https://doi.org/10.3390/ani12030262.
7. Lautz LS, Jeddi MZ, Girolami F, et al. Metabolism and pharmacokinetics of pharmaceuticals in cats (Felix sylvestris catus) and implications for the risk assessment of feed additives and contaminants. Toxicology Letters 2020; 338: 114-127. https://doi.org/10.1016/j.toxlet.2020.11.014.
8. Shrestha B, Reed JM, Starks PT, et al. Evolution of a Major Drug Metabolizing Enzyme Defect in the Domestic Cat and Other Felidae: Phylogenetic Timing and the Role of Hypercarnivory. PloS ONE 2011; 6(3): 1-11 . https://doi.org/10.1371/journal.pone.0018046.
9. Court MH. Feline drug metabolism and disposition: pharmacokinetic evidence for species differences and molecular mechanisms. The Veterinary clinics of North America Small animal practice 2013; 43(5): 1039–1054. https://doi.org/10.1016/j.cvsm.2013.05.002.
10. Lynch A, Shaw H and Milton GW. Effect of aspirin on gastric secretion. GUT 1964; 5(3): 230-236. https://doi.org/10.1136/gut.5.3.230.
11. Montinari MR, Minelli S, De Caterina R. The first 3500 years of aspirin history from its roots – A concise summary. Vascular Pharmacology 2018; 113: 1-8. https://doi.org/10.1016/j.vph.2018.10.008
12. Gupta RC. Veterinary Toxicology: Basic and Clinical Principals, 3rd ed. London, UK: Academic Press of Elsevier; 2018.
13. Stone E. XXXII. An account of the success of the bark of the willow in the cure of agues. In a letter to the Right Honourable George Earl of Macclesfield, President of R. S. from the Rev. Mr. Edward Stone, of Chipping-Norton in Oxfordshire. Philosophical Transactions of the Royal Society of London 1763; 53: 195-200. https://doi.org/10.1098/rstl.1763.0033
14. Awtry EH, Loscalzo J. Aspirin. Circulation 2000; 101(10): 1206-1218. https://doi.org/10.1161/01.CIR.101.10.1206.
15. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature: New biology, 1971; 231(25): 232-235. https://doi.org/10.1038/newbio231232a0
16. Karademir Ü, Boyacıoğlu M. Nonsteroidal Antiinflamatuvar İlaçların Kedi ve Köpeklerde Etkili ve Güvenli Kullanımı. Journal of Faculty of Veterinary Medicine, Erciyes University 2014; 11(2): 137-143.

17. Lascelles BDX, Court MH, Hardie EM, et al. Nonsteroidal anti-inflammatory drugs in cats: a review. Veterinary Anaesthesia and Analgesia 2007; 34: 228-250. https://doi.org/10.1111/j.1467-2995.2006.00322.x.
18. Maddison JE, Page SW and Church DB. Small Animal Clinical Pharmacology, 2nd ed. Edinburgh: Saunders Elsevier; 2008.
19. Whalan JE. A Toxicologist's Guide to Clinical Pathology in Animals: Hematology, Clinical Chemistry, Urinalysis, Switzerland: Springer International; 2015.
20. Wallig MA, Haschek WM, Rousseaux CG, et al. Fundamentals of Toxicologic Pathology, 3rd ed. London: Academic Press, Elsevier; 2018.
21. Penny RH, Carlisle CH, Prescott CW, et al. Effects of aspirin (acetylsalicylic acid) on the haemopoietic system of the cat. The British veterinary journal 1967; 123(4): 154-161. https://doi.org/10.1016/s0007-1935(17)40054-6.
22. D'Agati V. Does aspirin cause acute or chronic renal failure in experimental animals and in humans?. American Journal of Kidney Diseases 1996; 28(1): S24-S29. https://doi.org/10.1016/S0272-6386(96)90565-X.
23. Konturek SJ, Radecki T, Brzozowski T, et al. Aspirin-induced gastric ulcers in cats. Prevention by prostacyclin. Digestive diseases and sciences 1981; 26(11): 1003-1012. https://doi.org/10.1007/BF01314763.
24. Bugat R, Thompson MR, Aures D, et al. Gastric mucosal lesions produced by intravenous infusion of aspirin in cats. Gastroenterology 1976; 71(5): 754-759.
25. Satoh H, Amagease K and Takeuchi K. The role of food for the formation and prevention of gastrointestinal lesions induced by aspirin in cats. Digestive diseases and sciences 2013; 58(10): 2840-2849. https://doi.org/10.1007/s10620-013-2725-7.
26. Hansen DG, Aures D and Grossman MI. Histamine augments gastric ulceration produced by intravenous aspirin in cats. Gastroenterology 1978; 74(3): 540-543.
27. Hansen DF, Aures D and Grossman MI. Comparison of Intravenous and Intragastric Aspirin in Production of Antral Gastric Ulcers in Cats. Proceedings Of The Society For Experimental Biology And Medicine 1980; 164(4): 589-592. https://doi.org/10.3181/00379727-164-40921.
28. Svanes K, Leiknes KA, Varhaug JE, et al. Aspirin damage to ischemic gastric mucosa in shocked cats. Scandinavian journal of gastroenterology 1979; 14(5): 633-639. https://doi.org/10.3109/00365527909181402.
29. Feldberg W, Gupta KP, Milton AS, et al. Effect of pyrogen and antipyretics on prostaglandin activity in cisternal c.s.f. of unanaesthetized cats. The Journal of Physiology 1973; 234(2): 279-303. https://doi.org/10.1113/jphysiol.1973.sp010346.
30. Hardie EM. Management of Osteoarthritis in Cats. Veterinary Clinics of North America: Small Animal Practice 1997; 27(4): 945-953. https://doi.org/10.1016/S0195-5616(97)50088-X.
31. Lunsford KV, Mackin AJ. Thromboembolic therapies in dogs and cats: an evidence-based approach.T he Veterinary clinics of North America: Small animal practice 2007; 37(3): 579-609. https://doi.org/10.1016/j.cvsm.2007.01.010.
32. Hogan DF, Fox PR, Jacob K, et al. Secondary prevention of cardiogenic arterial thromboembolism in the cat: The double-blind, randomized, positive-controlled feline arterial thromboembolism; clopidogrel vs. aspirin trial (FAT CAT). Journal of veterinary cardiology: the official journal of the European Society of Veterinary Cardiology 2015; 17(1): S306-S317. https://doi.org/10.1016/j.jvc.2015.10.004.
33. Etscheidt J, Shahien A, Gainey M, et al. Review of Therapeutic Options for the Prevention of VTE in Total Joint Arthroplasty. Geriatrics 2020; 5(1): 1-15. https://doi.org/10.3390/geriatrics5010018.
34. Bilgic B, Tarhan D, Ekiz B, et al. The effect of pimobendan and enalapril use on blood serum trace element levels in dogs with myxomatous mitral valve disease. Journal of Trace Elements and Minerals 2023, 4: 1-8. https://doi.org/10.1016/j.vph.2018.10.008.
35. Sedláčková K, Száková J, Načeradská M, et al. Essential microelement (copper, selenium, zinc) status according to age and sex in healthy cats. Acta veterinaria Hungarica 2022; 70(4): 296-304. https://doi.org/10.1556/004.2022.00036.
36. Rishniw M. How much protection does clopridogrel provide to cats with hypertrophic cardiomyopathy?. Journal of the American Veterinary Medical Association 2024; 1-3. https://doi.org/10.2460/javma.24.04.0269.
37. Ho KH, Abrams-Ogg AC, Wood RD, et al. Assessment of platelet function in healthy cats in response to commonly prescribed antiplatelet drugs using three point-of-care platelet function tests. Journal of feline medicine and surgery 2017; 19(6): 638-647. https://doi.org/10.1177/1098612X16648182.
38. Blais MC, Bianco D, Goggs R, et al. Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE): Domain 3-Defining antithrombotic protocols. Journal of veterinary emergency and critical care 2019; 29(1): 60-74. https://doi.org/10.1111/vec.12795.

39. Borgeat K, Wright J, Garrod O, et al. Arterial thromboembolism in 250 cats in general practice: 2004-2012. Journal of veterinary internal medicine 2014; 28(1): 102-108. https://doi.org/10.1111/jvim.12249.
40. Çolakoğlu EÇ, Alihosseini H, Haydardedeoğlu AE. Hipertrofik Kardiyomyopatili Kedilerde Trombosit ve Ortalama Trombosit Hacmi Düzeyleri Erken Emboli Oluşumunu Belirlemede Kullanılabilir mi?. Harran Üniversitesi Veteriner Fakültesi Dergisi 2018; 7(1): 84-88. https://doi.org/10.31196/huvfd.470810.
41. Greenway CV, Murthy VS. Mesenteric vasoconstriction after endotoxin administration in cats pretreated with aspirin. British journal of pharmacology 1971; 43(2): 259-269.
42. Hall RC, Hodge RL, Irvine R, et al. The effect of aspirin on the response to endotoxin. The Australian journal of experimental biology and medical science 1972; 50(5): 589-601. https://doi.org/10.1038/icb.1972.52.
43. Riciotti E, Wangensteen KJ, FitzGerald GA. Aspirin in hepatocellular carcinoma. Cancer Research 2021; 81(14): 3751-3761. https://doi.org/10.1158/0008-5472.CAN-21-0758.
44. Kim MY, Han YM, Park JM, et al. GI-Safer Aspirin: Sometimes Sugar Coating Helps. Digestive diseases and sciences 2016; 61(8): 2151-2153. https://doi.org/10.1007/s10620-016-4236-9.
45. Rawlings CA, Farrell RL, Mahood RM. Morphologic changes in the lungs of cats experimentally infected with Dirofilaria immitis: Response to aspirin. Journal of veterinary internal medicine 1990; 4(6): 292-300. https://doi.org/10.1111/j.1939-1676.1990.tb03126.x.
46. Daş N, Nebioğlu S. Vitamin C aspirin interactions in laboratory animals. Journal of clinical pharmacy and therapeutics 1992; 17(6): 343-346. https://doi.org/10.1111/j.1365-2710.1992.tb01315.x
47. Dion PD. Feline aortic thromboemboli and the potential utility of thrombolytic therapy with tissue plasminogen activator. The Veterinary clinics of North America. Small animal practice 1988; 18(1): 79-86. https://doi.org/10.1016/s0195-5616(88)50008-6.
48. Keimowitz RM, Pulvermacher G, Mayo G, et al. Transdermal modification of platelet function. A dermal aspirin preparation selectively inhibits platelet cyclooxygenase and preserves prostacyclin biosynthesis. Circulation 1993; 88(2): 556-561. https://doi.org/10.1161/01.cir.88.2.556
49. Hawthorne AB, Mahida YR, Cole AT, et al. Aspirin-induced gastric mucosal damage: prevention by enteric-coating and relation to prostaglandin synthesis. British journal of clinical pharmacology 1991; 32(1): 77-83. https://doi.org/10.1111/j.1365-2125.1991.tb05616.x.
50. Clerici B, Cattaneo M. Pharmacological Efficacy and Gastrointestinal Safety of Different Aspirin Formulations for Cardiovascular Prevention: A Narrative Review. Journal of cardiovascular development and disease 2023; 10(4): 1-11. https://doi.org/10.3390/jcdd10040137.
51. Johnston SA, Leib MS, Forrester SD, et al. The effect of misoprostol on aspirin-induced gastroduodenal lesions in dogs. Journal of veterinary internal medicine 1995; 9(1): 32-38. https://doi.org/10.1111/j.1939-1676.1995.tb03269.x.
52. Tarnawski AS, Caves TC. Aspirin in the XXI century: its major clinical impact, novel mechanisms of action, and new safer formulations. Gastroenterology 2004; 127(1): 341-343. https://doi.org/10.1053/j.gastro.2004.05.037