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Oxalate Toxicoses in Pets: A Comparison of Conventional and Alternative Medicine

Oxalátmérgezés társállatokban: hagyományos és alternatív gyógymódok összehasonlítása

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Abstract

This work deals with the causes of oxalate poisoning in animals, examining specific plant species and other sources of oxalate ions such as ethylene glycol, which can seriously affect both pets and food-producing animals. I examined the symptoms of oxalate poisoning, which can appear suddenly, develop quickly, or take a long time to manifest depending on the animal species, diet, and the type of oxalate crystals involved. I collected and classified diagnostic options of oxalate intoxication and compared conventional treatments with alternative methods like homeopathy and phytotherapy. Historical treatments for oxalate poisoning focused on promoting urinary oxalate excretion and crystal formation. While such conventional treatments combined with modern technologies (intracorporeal laser lithotripsy, electrohydraulic lithotripsy, extracorporeal shockwave lithotripsy, ultrasonic lithotripsy) are prioritized, alternative therapies, like homeopathy and phytotherapy are also being explored. Some fruit juices and plant extracts might help enhancing calcium oxalate excretion and prevent the formation of urinary stones, though more research is needed to understand their effectiveness. Preventive strategies include the management of the animal's diet and the education of pet owners about the potential threats of oxalate-producing plants.

Absztrakt

Dolgozatomban az állatok oxalátmérgezésének forrásait vizsgáltam, melynek során számos olyan növényfajt és vegyszert (pl. etilén-glikolt) gyűjtöttem össze, amelyek mind kiskedvenceinket, mind haszonállatainkat veszélyeztethetik. Sorra vettem az akut és a krónikus oxalátmérgezés tüneteit, melyek hamar jelentkezhetnek, ill. hosszabb idő alatt is kialakulhatnak az állat fajától, étrendjétől és az aktuálisan szóban forgó oxalátkristályok típusaitól függően. Összegyűjtöttem és csoportosítottam a kapcsolódó diagnosztikai lehetőségeket, hogy az oxalátmérgezés hagyományos, valamint alternatív (fitoterápiás, ill. homeopátiás) kezelési módjait összehasonlíthassam. Az oxalátmérgezés korábbi kezelési módjai főleg a húgyutakban kialakuló oxalátkristályok kialakulásának megelőzését célozták, vagy azok vizelettel történő távozását próbálták megsegíteni. Napjainkban is főleg ezen módszerek alkalmazását részesítik előnyben, de modern technológiai vívmányokkal (pl. intrakorporális elektrohidraulikus, lézeres, ultrahangos, ill. extrakorporális lökéshullám litotripsziával) kombinálják őket. Az alternatív kezelési módok mint a homeopátia, vagy a fitoterápia módszereit az utóbbi években kezdték (újra) felfedezni. Bizonyos gyümölcslevek és növényi kivonatok megsegíthetik a kálcium-oxalát-kristályok kiválasztását és elejét vehetik húgyúti kövek képződésének, de hatásosságuk bebizonyításhoz, valamint hatásmechanizmusaik megértéséhez még további vizsgálatok szükségesek. Megelőzésként fontos az állatok étrendjének célirányos összeállítása, valamint a gazdák ismereteinek kibővítése főleg az oxalátkristályokat termelő növényfajok jelentette veszélyekkel kapcsolatban.

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1. Introduction

Oxalate ($[C_2O_4]^{2-}$) is the anion of oxalic acid ($[COOH]_2$) in aqueous solutions from which harmful oxalate crystals can form in animal tissues [1]. This process involves the combination of dietary oxalate and positive physiological electrolytes such as sodium (Na^+) and potassium (K^+), as well as other essential ions like calcium (Ca^{2+}) and magnesium (Mg^{2+}) [2].

Water-soluble oxalates are usually mechanically harmless when ingested but as soon as they get solved then absorbed, they may build water-insoluble salts with blood plasma divalent cations (Ca^{2+}, Mg^{2+}). This can cause two types of problems: a) the formation of oxalate crystals within blood vessels [3] and/or renal tubules [4] causing blockage and mechanical damages, and b) the development of hypocalcaemia and hypomagnesaemia by eliminating Ca^{2+} and Mg^{2+} ions from bloodstream [5, 6]. With these divalent cations, plants can directly form water-insoluble, sharp oxalate crystals (e.g., raphides). Such crystals, when ingested, can penetrate buccal mucous membranes causing local irritation, hypersalivation, oedematous lips and tongue, and oropharynx with laryngospasms, drooling at the mouth/muzzle, gagging, colic, bloody diarrhoea, depression/prostration, sometimes even death by reason of asphyxia or bleeding in the gastrointestinal tract [7, 8]. They are usually mechanically dangerous because they often form sharp edges, such as large prismatic (rhomboid), elongated, rectangular or styloid (needle like) crystals. Sometimes, they even form needle bundles (like raphides). The small, angular types, like druses, can cause blockage in blood vessels [9]. The best way of preventing such conditions is providing enough water to our pet and feeding it with oxalate-free foods [10].

Depending on the amount of oxalate crystals ingested and the length of time period the animal is exposed to dietary oxalates, the level of intoxication varies. In addition to the amount and exposure time, its severity also depends on the quality of oxalate-containing food consumed and the species identity, age, gender, and general health conditions of animal individuals [11, 12, 13, 14].

Oxalate crystals (oxalic acid) are naturally biosynthesized by several plant species belonging to various plant families. The members of family Agavaceae, Amaranthaceae, Araceae, Cactaceae, Chenopodiaceae, Euphorbiaceae, Mesebryanthemaceae, Oxalidaceae, Poaceae, Polygonaceae, as well as some fungal taxa can be rich in oxalate crystals [1, 11, 15, 16, 17, 18, 19, 20]. Moreover, species from family Araceae and Euphorbiaceae form the sharp, water-insoluble oxalate crystals (the raphides) causing even mechanical injuries in

tissues. There are over 200 plant species in family Araceae. These plants are mostly shade-tolerant, fast-growing, frost sensitive tropical herbs with wide tolerances to soil properties and therefore, frequently applied as indoor ornamentals [21]. Within this family, members of genera *Dieffenbachia* and *Philodendron* are among the most popular pot plant species [22]. The most common araceous taxa with a significant amount of oxalate crystals are listed in **Table 1**. In addition to these species, some food plants of human importance also contain calcium oxalate crystals, such as spinach (*Spinacia oleracea*) and sorrels (*Rumex* spp.) [23]. Human food plants with high oxalate crystal contents are collected in **Table 2**. The amount of oxalate crystals varies according to plant species, and within the same plant individual, among organs and along growing seasons [24].

Table 1. Common household ornamental plant species biosynthesizing oxalate crystals (following [1, 25]).

Plant taxa	**Common name(s)**
Aglaonema spp.	Chinese evergreen
Alocasia spp.	elephant's ear, giant taro
Amaryllidaceae spp.	narcissus, jonquil
Anthurium spp.	flamingo plant, calla lily, arum lily, pig lily, lirio calla
Arisaema spp.	jack in the pulpit, Indian turnip, green dragon, dragon root
Arum spp.	arum, cuckoo-pint, lords and ladies
Caladium spp.	caladium, angel's wings, caladio, cananga
Calla palustris	wild calla, white arum, water arum, bog arum, water dragon
Colocasia spp.	elephant's ear, taro, dasheen, kalo, tayo bambou, malanga, cocoyam
Dieffenbachia spp.	dumb cane, camilichigui, americanarum, poison arum
Epiprenum spp.	pothos, golden pothos, hunter's robe, ivy arum, devil's ivy
Monstera spp.	ceriman, fruit salad plant, bread fruit, Swiss cheese plant, window leaf plant, hurricane plant
Philodendron spp.	philodendron, money plant, sweetheart vine
Pistia stratiotes	water lettuce, floating lettuce, shell flower
Spathiphyllum spp.	peace lily
Syngonium (*Nephthytis*) spp.	arrowhead vine, goose foot
Xanthosoma spp.	elephant's ear, cocoyam, malanga, tannia
Zantedeschia spp.	calla lily, arum lily, pig lily, lirio calla

A substantial body of literature covers the cases and clinical signs of oxalate toxicosis (see chapter 4.2.), but less information is available on the treatments (chapter 4.8.). There is a need for reviews that summarize potential treatments and compare traditional and alternative methods. Additionally, studies on the harmful threshold levels of oxalate crystals for various livestock species and pets and their tolerance to oxalate toxicosis are scarce [29]. Given these gaps in knowledge, I have outlined my objectives in the next chapter.

Table 2. Human edible plants with oxalate levels exceeding 300 mg per 100 g. (following [26, 27, 28]).

Plant name	**Oxalate (mg)**
Parsley, raw	1,700
Chives, raw	1,480
Purslane, raw	1,310
Cassava root, raw	1,260
Amaranth leaves, raw	1,090
Spinach, raw	970
Beetroot, boiled	675
Cocoa powder	623
Beet leaves, raw	610
Carrot, raw	500
Soy protein	496
Radish, raw	480
Collards, raw	450
Black pepper	419
Soy nuts (28.3 g)	392
Brussels sprouts, raw	360
Garlic, raw	360
Lettuce, raw	330
Watercress, raw	310

2. Objectives

I aimed to:

- review both past and present literature on oxalate toxicosis in pets and livestock;
- compare traditional treatments with currently used ones, and alternative approaches like phytotherapy and homeopathy;
- collect the most common sources of oxalate toxicity (plant taxa, household chemicals);
- discuss diagnostic methods and preventive measures;
- rank livestock and pet species by their tolerance to plant oxalate crystals and oxalic acid.

3. Materials and Methods

To obtain literature data, I used scientific handbooks and peer-reviewed papers browsing:

- ScienceDirect (https://www.sciencedirect.com/),
- Google scholar (https://scholar.google.com/),
- PubMed (https://pubmed.ncbi.nlm.nih.gov/),
- ResearchGate (https://www.researchgate.net/),
- and the library of University of Veterinary Medicine Budapest (Hutÿra Ferenc Library, Archives and Museum).

4. Results

4.1. A short overview of plant taxa producing oxalate crystals

According to poison control centres worldwide, *Dieffenbachia* species (family Araceae) cause plant oxalate intoxications the most frequently in pets [30]. Focusing on genus *Dieffenbachia*, several case studies were reported since the 90ties, e.g., [7, 31, 32, 33] but other ornamental plant species from this family (**Table 3**) can also be dangerous to pets [25]. Furthermore, the intoxication with *Epiprenum* spp., *Spathiphyllum* spp., and *Zantedeschia* spp. [34], as well as *Aglaonema commutatum*, *Monstera deliciosa*, *Philodendron* spp., and *Syngonium podophyllum* [35, 36] were documented in canidae in the past.

Table 3. An annotated checklist of key oxalate-containing plant taxa from the Northern Hemisphere [25, 36, 37, 38, 39, 40].

Plant family	Plant taxa	Average height (m)	Toxic parts
Amaranthaceae	*Halogeton glomeratus*	0.3	leaves, stems, roots
Amaryllidaceae	*Allium* spp.	0.8	bulbs, leaves
Apocynaceae	*Cynanchum acutum*	3	stems, leaves
Araceae	*Aglaonema* spp.	0.9	stems, leaves
	Dieffenbachia spp.	3	stems, leaves
	Epipremnum spp.	18	stems, leaves
	Monstera spp.	1.4	stems, leaves, aerial roots
	Philodendron spp.	0.9	stems, leaves
	Spathiphyllum spp.	0.9	petals, stems, leaves, pollen grains
	Syngonium spp.	1.8	stems, leaves
	Zantedeschia spp.	0.9	stems, leaves
Caryophyllaceae	*Saponaria officinalis*	0.8	stems, leaves, seeds
Hypericaceae	*Hypericum perforatum*	1	stems, leaves, flowers
Papaveraceae	*Chelidonium majus*	0.7	all parts
Polygonaceae	*Rumex acetosa* and other *Rumex* spp.	0.6	leaves

Ruminants in North America and Central Asia are significantly affected by consuming large quantities of *Halogeton glomeratus* (Amaranthaceae family), a sodium oxalate-producing plant species selective for highly saline grasslands [41].

Under rapid growth conditions, grasses (Poaceae species, e.g., *Setaria* spp. and *Panicum* spp., from Europe) can also be rich in oxalate crystals (exceeding 6% in dry weight) and bind a notable amount of dietary Ca^{2+} to form calcium oxalate [42]. Non-European grass taxa like *Megathyrsus maximus*, *Pennisetum* spp., *Cenchrus ciliaris*, and *Digitaria* spp. are also known as efficient oxalate-accumulating species. Members of other plant families, e.g., *Cynanchum acutum* (Apocynaceae), *Chelidonium majus* (Papaveraceae), *Saponaria officinalis* (Caryophyllaceae), *Hypericum perforatum* (Hypericaceae), and *Rumex acetosa* (Polygonaceae) often cause chronic intoxications in horse [42, 43, 44, 45, 46, 47].

4.1. Functions and formation of oxalate crystals in plants

4.1.1. Biological functions

Crystal formation within plants can provide several biological functions like a mechanical support or protection of plant cells against herbivory [9], but also a light gathering (collecting) function in shady environments [48, 49] or even a light reflecting role in extremely sunny habitats [9]. Several papers focus on the physiological functions of plant crystals (e.g., [9, 48, 50]). They hypothesized their roles in the regulation of Ca^{2+} levels within the plant and the maintenance of cellular Na^{+} and K^{+} balance [48, 50]. Formation of intracellular crystals from ions of toxic metals such as aluminium, lead, strontium, and cadmium [50, 51] can result chemically inactive, water insoluble salts not harmful to plant metabolic processes [52, 53, 54, 55, 56]. Another theory suggests that calcium oxalate crystals are waste products and are accumulated in elderly leaves before leaf fall [57]. Plant crystals produced against herbivory are usually stored in vacuoles of specialized cells known as idioblasts (**Figure 1**).

4.1.2. Biosynthesis

Numerous pathways of oxalate biosynthesis have already been described in plants. For example, in the plant species Pistia stratiotes and Medicago truncatula [58], the conversion of L-galatonolactone to ascorbic acid, is facilitated by the enzyme L-galactono-γ-lactone dehydrogenase, localized in the inner mitochondrial membrane, ultimately results oxalic acid [50, 59]. Another pathway entails the conversion of isocitric acid to glyoxylic acid driven by the enzyme isocitrate lyase in *Oxalis pes-caprae*. It is followed by a subsequent conversion to oxalic acid and glycollic acid with the help of another enzyme: NADP-linked glyoxylate re-

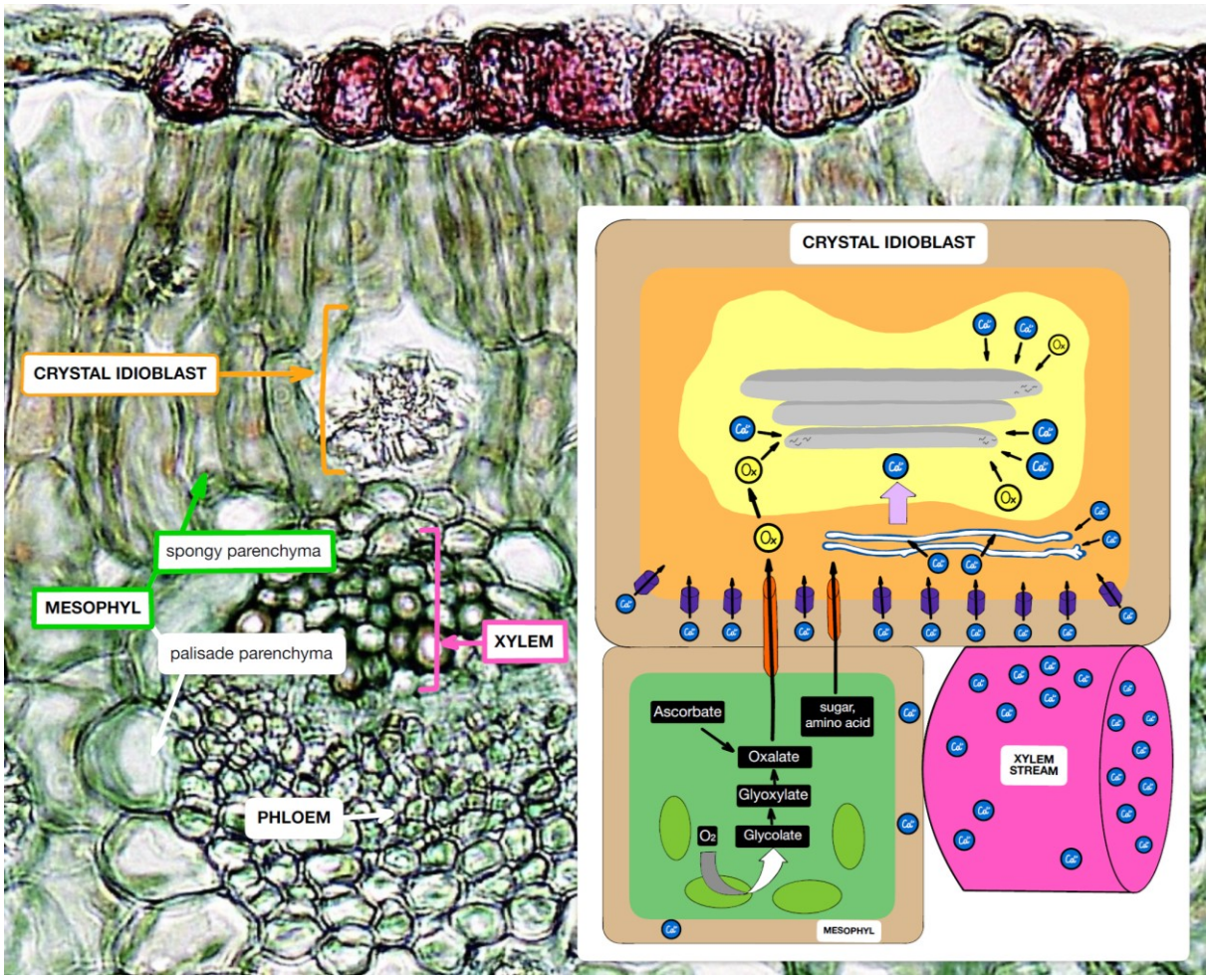

Figure 1. Calcium oxalate formation in crystal idioblasts – raphide crystal model. (based on [9])

ductase [60]. In *Pistia stratiotes*, L-ascorbic acid (AsA) was identified as the primary carbon source for the oxalic acid used in crystal formation [9]. Crystal idioblasts, where these processes are completed, are equipped not only for the rapid uptake and storage of calcium ions but also for producing the oxalic acid necessary for these metabolic processes [61]. In other cases, oxalate crystals can be transported into the vacuoles across numerous crystal membrane chambers in which the formation of crystals takes place [62]. Here, the crystals are enclosed by a lamellar sheath that is found between the crystal and the vacuole tonoplast. This sheath, along with the fusion with the tonoplast membrane and the plasmalemma, isolates the crystals from the metabolic processes of cytoplasm [63]. In all, oxalate crystals are biosynthesized via secondary (taxon specific) metabolic processes to regulate plant cytoplasmic Ca^{2+} levels and, by consuming its intermediers, to equilibrate primary (universal) metabolic processes vital for plant survival.

4.2. Clinical signs of oxalate toxicosis in animals

Clinical signs of oxalate toxicosis are shaped by numerous factors. These factors are never independent to each other, always acting simultaneously and with varied effect sizes among individuals resulting a wide variety of, and difficult-to-interpret clinical symptoms. The oxalate absorption level, which determines the severity of oxalate poisoning, is influenced by the actual oxalate crystal concentration (pH dependent) and chemical composition of plant sap, as well as the feeding habits and gastrointestinal morphology of the animal species [1, 25].

For example, oxalate toxicity produces distinct clinical symptoms in monogastric animals versus ruminants due to differences in their metabolic activities. In monogastric animals, dietary oxalates are initially exposed to the highly acidic stomach, where these crystals dissolves, oxalic acid is formed, that can be taken up easily. In the alkaline environment of small intestine, calcium ions can readily bind to oxalate ion hindering their absorption and leading to hyperoxaluria [64]. Ruminants can tolerate higher levels of oxalate salts in forages due to the activity of rumen bacteria. In the rumen, *Oxalobacter formigenes* breaks down oxalate ions with the help of coenzyme A and ATP [65]. In contrast, cats are considered to be “true carnivores” [66], therefore they are less likely to get intoxicated by dietary oxalate crystals compared to dogs, which tend to consume a significant amount of plant materials [34, 67]. However, it was reported that fibrous grasses consumed by cats can alleviate clinical signs. Vomiting, evoked by fibrous plant materials, can help expelling hairballs and decrease the population size of gastrointestinal parasites [68, 69]. Therefore, in flats where fibre-rich grasses are unavailable, cats often resort to ingest dangerous ornamental plants. This behaviour is evidenced by their consumption of oxalate-rich plants, such as daffodils [70], dumb cane [7] or certain lily species [37, 71].

In the following subchapters, a classification of clinical signs of oxalate poisoning (peracute, acute, chronic) is given with special attention to the elapsed time after the exposure to oxalate crystals.

4.2.1. Peracute toxicosis

Peracute oxalate toxicosis occurs within minutes to hours after exposure or consumption of plants rich in oxalate crystals. When the oxalate-containing plants are chewed by animals, masses of raphides can penetrate the mucous membranes of their mouth leading to irritation and discomfort in the whole oropharyngeal region [25]. In dogs, the inflamed, oedematous

mucous membranes can even result dyspnoea and airway obstruction [32]. Excessive salivation, diarrhoea, vomiting with blood, and apathy were also highlighted [7]. Pedaci et al. [30] reported behavioural abnormalities, such as head shaking, pawing, rubbing, and vocalization connected to pain short after the exposure to dietary oxalate crystals.

Dullness, head lowering, inappetence, coughing accompanied by white foam around the mouth and reluctance to follow the flock are the first signs described to appear in sheep four hours after the ingestion of *Halogeton glomeratus* [72].

4.2.2. Acute toxicosis

Signs of a one-time high dose (acute) oxalate toxicosis established 24 hours after the consumption of oxalate rich plants are detailed here.

Elimination of divalent cations (Ca^{2+} and Mg^{2+}) from blood plasma can cause severe hypocalcaemia and hypomagnesaemia in each animal species [73]. Oxalate crystal deposition in small blood vessels throughout the brain, heart, liver, intestinal mucosa, and kidneys, coupled with a decrease in serum Ca^{2+} levels, impairs the activity of muscle cells [74]. This condition can lead to neuromuscular excitation, resulting in muscle tremors, muscle fasciculations, tetany, or instead, flaccid paralysis, and potentially death [14, 75].

The phenomenon of hypocalcaemia can be observed particularly well in cattle experiencing mild intoxication, which leads to subacute locomotor difficulties that are generally not life-threatening [76, 77]. Sheep can become comatose and eventually die after developing more serious clinical signs like ataxia of the hind limbs, rapid breathing, and recumbency [72]. In an experimental study by James et al. [78], low *Halogeton* diets, containing 3.2% soluble oxalates, caused mild hypocalcemia, increased water intake and raised the ruminal, as well as the urinary pH in the members of a sheep herd. In more severe cases, sheep can show hypersensitivity to oxalate overload, presenting symptoms such as decreased feed intake, apathy, xerostomia, dyspnoea, reduced rumen motility, obstipation, and occasionally seizures [79].

Acute poisoning characterized by hypocalcemia has not been reported as frequently in equines as in ruminants because horses are selective eaters and therefore rarely ingest anything irritant [80]. However, a 4-year-old foal was referred to the clinic with permanent stiffness for several days and refusing to drink water for a day. The observed clinical signs were uncoordinated walking showing minor compulsive movements, stiff hindquarters, slight dragging of both hooves on the hind limbs, wide holding of front legs, lowered head, raised

lips and wrinkled nose. The foal had almost absent bowel sounds on auscultation of the abdomen and developed a negative reaction on vision & threat reflexes. Laboratory examinations revealed a decrease in ionized calcium level of 0.54 mmol/l compared to the normal amounts of 1.4–1.7 mmol/l and in a total urinal calcium level of 1.38 mmol/l (normal: 2.8–3.2 mmol/l). It turned out that the foal grazed on a pasture with many forbs including sorrels (*Rumex* spp.) with a high oxalate content of more than 0.5% in weight [81].

In small animals, clinical manifestations of acute intoxication include keratoconjunctivitis resulting from ocular contact with the plant sap, characterized by fine blue crystal depositions in the corneal stroma and conjunctival chemosis [19, 25, 82]. Severe symptoms in cats have been reported like extensive gastric ulceration (**Figure 2A**) and hematemesis after the consumption of *Dieffenbachia* spp. (**Figure 2B** [7]. Also, for cats, Fitzgerald [37] reported acute renal failure and polyuria resulting in severe dehydration appearing 12 to 30 hours after the ingestion of *Spathiphyllum* spp. Ingestion of oxalate-rich plants can induce moderate to severe gastritis in a dose-dependent manner [83] along with anorexia and depression that persist throughout the entire clinical condition [37]. The Amaryllidaceae species can frequently cause contact dermatitis, due to the embedding of calcium oxalate raphides into the skin tissues [84]. Additional general clinical signs, such as lethargy, muscle tremors, coughing, and stiff limbs were also documented [85].

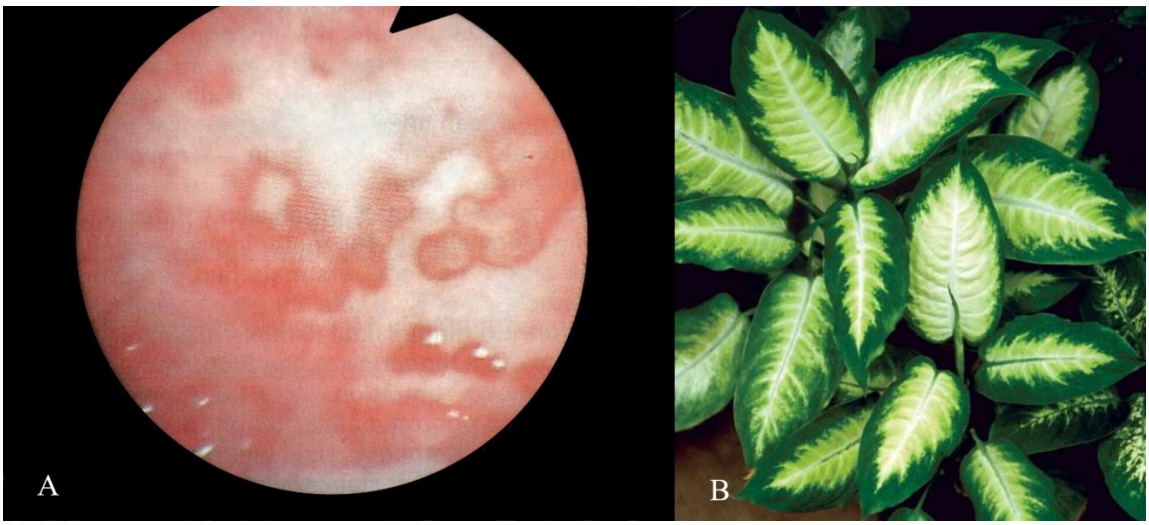

Figure 2. (A) Endoscopy of gastric ulceration in a cat after *Dieffenbachia* intoxication [7]. (B) *Dieffenbachia sequine* [25].

4.2.3. Chronic toxicosis

A low level of, but long-term (chronic) toxicosis can take months or even years to develop. As previously mentioned, oxalate reduces the bioavailability of vital positive ions (electrolytes: K^+, Na^+ and minerals: Ca^{2+}, Mg^{2+}). Following the sudden decrease of blood Ca^{2+} level, the parathyroid hormone (PTH) is started to be secreted which catalyses the Ca^{2+} mobilization from bones [14, 86]. In horse, it can lead to chronic secondary nutritional hyperparathyroidism, also referred as osteodystrophia fibrosa, "bighead" or "bran disease" [43, 75]. There are three classical clinical manifestations related to this: ill-thrift, lameness, and the swelling of maxilla and mandible. However, symptoms may appear individually as sinusitis, or upper tract respiratory noise, watery nasal discharge, facial distortion [87], torn/detached ligaments and tendons, or subepiphyseal microfractures [88, 89]. The name "bighead" is relatable to severe cases of osteodystrophia fibrosa, which are expressed by mostly bilaterally developed changes in the skull bones, especially the jaws, maxilla, mandible, and nasal bones (**Figure 3A**). The distortion of mandible may induce separation of the upper and lower incisors so that the horse is less able to masticate short grasses (**Figure 3B**). Radiographic changes of bones like cortical radiolucent linear striations, endosteal roughening, and coarse trabeculation of spongy bone at the metaphyseal ends of medullary cavity were observed by Stewart et al. [42] (**Figure 3C**).

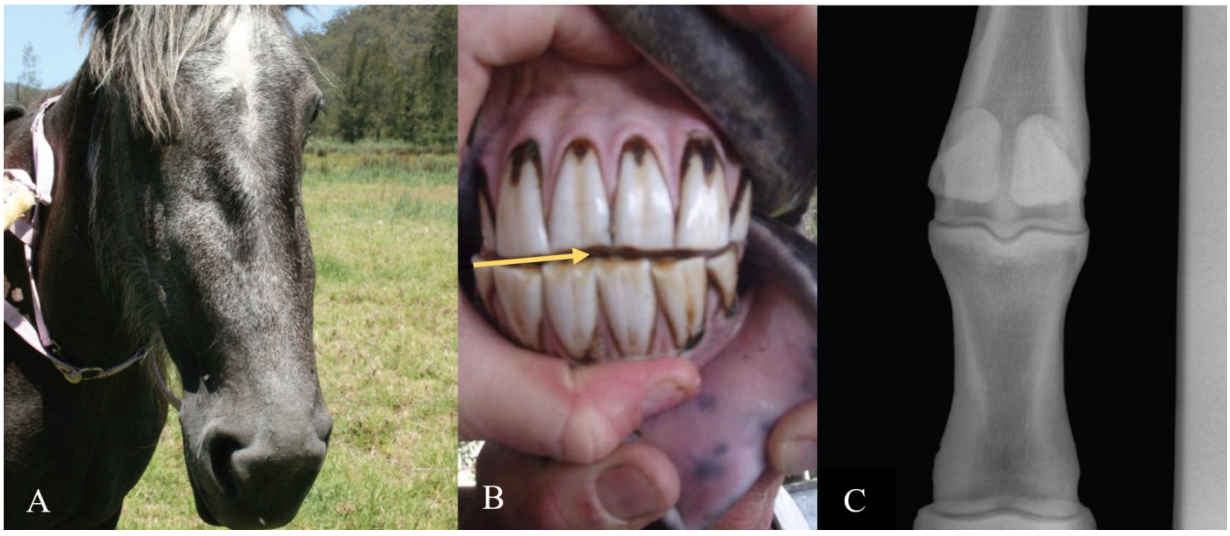

Figure 3. (A) A horse with swelling over the nasal bones and facial crests. (B) Separation of incisors due to the distortion of mandibula. (C) Fetlock radiograph in a horse with NSH (Nutritional Secondary Hyperparathyroidism); following Stewart et al. [42].

In small pets (dogs and cats), chronic intoxication may lead to the formation of nephroliths and uroliths within days to weeks, potentially progressing over three months to tubular and urinary tract obstructions. Fitzgerald [37] described anuria in cats occurring 24 to 48 hours post-ingestion, leading to the accumulation of metabolic waste and toxins. These progressions can cause nephron damage, renal fibrosis, and ultimately renal insufficiency consequentially leading to death [1] and [14]. Overall, poisoning of oxalate-containing plants can also be fatal for small pets but such animals are usually carnivorous hence, do not persist in chewing plants. In addition, the short onset of pain and inflammation induced by the raphides of several oxalate-producing plants can also make these animals stop chewing such plant taxa [25, 31].

Feeding ruminants with plants rich in oxalic acid has been also shown to negatively affect milk production and fat content [14, 90]. However, no studies have confirmed that oxalates could reduce calcium absorption from milk. Oxalate toxicosis in ruminants has been clinically associated with vascular necrosis and haemorrhages due to oxalate crystal formation within blood vessels [91].

A summary of clinical signs of oxalate intoxication in pets can be found in **Table 4**.

Table 4. Summary of frequently observed symptoms across pet species of oxalate intoxication.

Symptom type	Clinical signs
Peracute	*Dyspnea, airway obstruction* and *hypersalivation*: severe respiratory distress noted in **Canidae, Felidae** and **Capridae**, indicating systemic disease manifestation [7, 32, 72].
Acute	*Hypocalcaemia:* a critical condition observed in **Canidae**, **Felidae**, **Equidae**, **Bovidae**, and **Capridae**, presents with severe muscular and neurological symptoms such as tetany [5, 72, 73, 80, 85].
Subacute	*Locomotor difficulties*: detected in **Bovidae** and often started by underlying metabolic disorders or musculoskeletal problems. This symptom can signal chronic pain or weakness and thereby influence both health status/recovery and productivity [76, 77, 90].
Chronic	*Depression* and *anorexia*: these persistent symptoms are indicative of ongoing health issues within members of the **Canidae**, **Felidae**, and **Bovidae**, suggesting a systemic problem that requires long-term management [1, 7, 8, 37].
	Nephroliths and *uroliths*: these are commonly seen in **Canidae** and **Felidae**. If disease is not controlled, they may potentially progress to *tubular* and *urinary tract obstructions*, that can lead to serious complications such as acute renal failure, significant pain, and increased mortality risk [1, 8, 14, 23, 37, 71].

4.2.4. Pathological and histopathological changes

Intoxication from oxalate-containing plants manifests in various pathological and histopathological changes. Pathological investigations have revealed oedema and reddening of tongue [92], along with ulcerative stomatitis characterized by multifocal, symmetric bilateral ulcerations and necrosis on the ventral surface of tongue, with glossitis [71, 93]. An extensive gastric ulceration and severe dehydration were also noted. Dehydration often goes with the retraction of ocular globe in the orbit (7, 33, 71, 83]. Peterson et al. and Bates [32, 33] published the swelling of oropharyngeal region, tongue, and erythematous lips. Occasionally, contact dermatitis [83], stiff limbs [85], and ocular lesions characterized by corneal opacity and damage to the conjunctiva [19, 92] can be also observed. Additional pathological findings reveal lesions including oedema and enlargement of both kidneys in pets [71], while formation of uroliths have been documented for grazing animals [94].

Histopathologically, severe epithelial cell degeneration, abundant necrotic debris, and birefringent oxalate crystals in the proximal and distal convoluted tubules were observed [71]. Moderate white matter degeneration of the cerebellum and telencephalon, indicating lesions due to ataxia and seizures were also observed [71]. Oedema with diffuse vascular congestion, fragmented neutrophils throughout the tongue, proliferation of small vessels, and slight atrophy of some muscle fibres were observed in histological slides from an experiment on rats that ingested *Dieffenbachia* juice [92]. Peterson et al. [32] describes histological changes such as pronounced oedema and neutrophilic, lymphocytic, as well as mast cell infiltrations of the afflicted tissues.

In summary, the primary organs affected by intoxication from oxalate-containing plants include the kidneys, gastrointestinal tract, and oral cavity, with the most common symptoms across different animal species being oedema, ulcerative stomatitis, severe dehydration, and the formation of uroliths.

4.3. Mechanism of action of oxalate toxicosis

Van Kampen and James [3] suggest that vascular damage can result from elevated oxalate levels, leading to the formation of crystal deposits in the submucosal walls of small blood vessels. When a large amount of oxalate crystals/oxalic acid is ingested, the stomach or the rumen becomes overwhelmed, disrupting their ability to metabolize oxalate ions [14].

Consequently, the oxalate ion is absorbed from the intestines into the bloodstream, where, at high concentrations, binds with Ca^{2+} and Mg^{2+} to form salts insoluble in water. These oxalate crystals can be formed in the kidneys, obstructing urinary outflow [5, 14, 77, 95], and affect the gastrointestinal tract, as well as the neural tissues [96].

Oxalate crystal formation in the vascular system is influenced by blood pH, as well. Blood vessels farther from the lungs have higher CO_2 levels and a more acidic pH, making them less prone to crystal formation than vessels in well-perfused organs with more oxygen-rich, therefore more alkaline environments. Hence, oxalate crystals are frequently formed in vital organs like kidneys, eyes, mucous membranes, etc. [19, 25, 32, 71, 92].

As previously discussed, the oxalate ion tends to bind to various minerals such as calcium, iron [97] and magnesium leading to their deficiencies in the body. Elimination of divalent cations (Ca^{2+} and Mg^{2+}) from blood plasma can cause severe hypocalcaemia and hypomagnesaemia in every animal species [25, 73]. Mg^{2+} deficiency showed to be associated with increased oxidative stress markers, including oxidized lipids, proteins, and DNA [98]. DNA oxidation can be explained by the deficiency of ATP hydrolysis, which requires a Mg^{2+} ion for the formation of Mg^{2+}–ATP complex [99]. Furthermore, Mg^{2+} deficiency leads to a build-up of cytosolic Ca^{2+}, disrupting oxidative phosphorylation [98]. Research by Dickens et al. [100] showed that bovine endothelial cells grown in a low Mg^{2+} environment experienced heightened free radical-induced intracellular oxidation and cytotoxicity. Such oxidative stress can cause endoplasmic reticulum damage, ultimately leading to cell death [101]. Once exposed to oxalates, the cells undergo chemical changes, as the production of phosphatidylserine and the activation of phospholipase A2. These lead to the release of bioactive lipids, activation of caspases, and peroxidation of lipids which processes are part of the apoptosis [4, 25, 102, 103, 104].

Oxalate crystals may introduce other toxic substances from the plant, such as trypsin-like proteolytic enzymes. These enzymes can trigger the release of histamine and prostaglandins, resulting in the development of allergic reactions and local inflammation [25, 105].

4.4. Toxicokinetics

The toxicokinetics of oxalate intoxication has primarily been studied in humans but can be extrapolated to monogastric animals due to their similar metabolic processes. Ruminants are

less affected by oxalate toxicosis [8] because oxalate-degrading bacteria in the rumen increases significantly enough to avert oxalate poisoning [14].

Absorption of oxalate crystals via mucous membranes in the oral cavity or in the GI tract can be rapid in animals [7, 32, 83]. The absorption level depends on both the animal species and the amount and types of oxalate crystals in the plant species. Plant species may accumulate large amounts of both water-insoluble oxalate crystals (formed by Ca^{2+}, Mg^{2+}, and Fe^{2+}) and soluble ones (with $NH4^{+}$, Na^{+}, and K^{+}) [9]. According to Heaney and Weaver [106], the absorption of calcium oxalate from crude spinach is higher when combined with meals and takes place approximately five hours after ingestion. Oxalic acid is less absorbed than its crystals [29].

Distribution of oxalic acid with blood circulation is quick. Oxalic acid and its anion (oxalate) can reach all the tissues and form crystals.

Metabolism of oxalate crystals between monogastric animals and ruminants is highly different. Ruminants can exhibit greater tolerance to oxalate-containing plants due to the presence of a rumen bacterium, *Oxalobacter formigenes*, which degrades oxalic acid into CO_2 and formate, using formate as an energy source [8]. However, if the oxalic acid concentration exceeds a certain threshold, e.g., 69 g/kg according to Marais [97], it can also cause acute toxicosis in cattle as the rumen becomes overwhelmed and unable to convert the oxalic acid into its by-products.

Oxalic acid (oxalate ion) can be efficiently excreted via urine at 8–40 mg/day. Urinal excretion can be completed within the first 48 hours post-ingestion [37].

4.5. Ethylene glycol intoxication

It is important to note that ethylene glycol, the commonly applied antifreeze formulation, is toxic to animals because it is metabolised into oxalic acid and subsequently results in oxalate poisoning [107]. During its breakdown in the liver, ethylene glycol is first metabolised to glycoaldehyde by the enzyme alcohol dehydrogenase. Glycoaldehyde is then oxidised to glycolic acid, later to glyoxylic acid and finally to oxalic acid [108]. Ethylene glycol has an LD50 value of 6.6 ml/kg bw in dogs and 1.5 ml/kg bw in cats [109]. This makes ethylene glycol particularly toxic to cats, who are often intoxicated through cutaneous absorption and grooming. However, intoxications are more common in dogs, as they are attracted by its sweet taste [110].

4.6. Responses of different animal species and breeds to oxalate toxicosis

Concerning dogs and cats, oxalate poisoning is predominantly developed by the reason of accidental intake of ethylene glycol [109, 110]. However, a few cases of intoxication were reported due to plant oxalate crystals. Loretti et al. [31], from Brazil, reported oxalate poisoning in dog caused by *Dieffenbachia picta*. From the US, Peterson et al. [32] published a case study with a dog poisoned by *Dieffenbachia* sp. Müller et al. [7], in Switzerland, pointed *Dieffenbachia* spp. to be toxic to cats. One of the most recent case reports on *Dieffenbachia* poisoning in dog was published in Portugal by Torres et al. [85].

The developmental stage and age of animal individuals can modify the effects of oxalate crystals. Elderly dogs and cats are at a higher risk of developing uroliths due to dietary oxalate. The physiological changes associated with aging can alter the urinary environment, promoting crystal formation and stone development [111]. The formation of kidney stones can be breed-specific, as well. Pure-bred cats such as '*Burmese*', '*Himalayan*', '*Persian*' [112], and '*Ragdoll*' [113] are more likely to develop hyperoxaluria. In dogs, especially the small-bred ones like the '*Bichon Frise*', '*Brussels Griffon*', '*Cairn Terrier*', '*Chihuahua*', '*Jack Russell*', '*Japanese Chin*', '*Lhasa Apso*', '*Maltese*', '*Miniature Pinscher*', '*Miniature Schnauzer*', '*Pomeranian*', '*Yorkshire Terrier*' [114], '*Shih Tzu*' and the large-bred '*Keeshond*' were reported to be predisposed to calcium oxalate uroliths [115].

The gender of animals also influences their tolerance to oxalate crystals from forages. Male animals often develop nephroliths that can block the urethra [116, 117]. In contrast, females form kidney stones but their wider and shorter urinary tract allows the stones to pass more easily [118]. Consequently, males are more likely to exhibit symptoms.

In general, ruminants are less susceptible to oxalate toxicosis compared to monogastric animals. Experimentally exposing cattle and sheep to increased oxalate levels indicated an enhanced degradation of oxalate crystals by rumen bacteria [8, 65]. Ruminants that are accustomed to the constant presence of low levels of dietary oxalate crystals can develop higher tolerance against oxalate intoxication [119, 120]. Goats adapted to oxalic acid by the daily oral administration of 0.6 mmol/kg live weight oxalic acid were able to effectively establish an oxalate-degrading bacterial community [14, 121]. However, it was also seen that ruminants developed hypocalcaemia when they were tried to get accustomed to forages containing oxalate crystals [122]. A high level of dietary oxalate can negatively affect weight gain and milk production [90]. Rumen bacterial species like *Oxalobacter formigenes* [8], *Enterococcus faecalis*, and lactic acid bacteria are also capable of degrading Ca-oxalate [123].

Intestinal oxalate-degrading bacteria have also been detected in horse [124], although equidae are generally less efficient at breaking down oxalate crystals. Blaney et al. [125] conducted experiments and found that horses only mobilized 6.3% of the Ca^{2+} from dietary calcium oxalate.

The most cases of oxalate intoxication in horse turned out to promote a chronic Ca^{2+} deficiency due to the trapping of Ca^{2+} by oxalate ions in their lower alimentary tract. In the alkaline pH of the equine intestinal tract, Ca-oxalate is easily formed and the largest amount of ingested oxalate ions is utilized as a carbon source by caecal bacteria. However, the amount of Ca^{2+} released by bacterial activities in the hindgut is unavailable for absorption because the absorption of oxalate crystals take place in the small intestines [125, 126].

4.7. Diagnostic methods of oxalate intoxication and its prognosis

Dealing with an animal patient suspected of oxalate intoxication, the initial step should involve a thorough physical examination, including a visual assessment of its overall condition and a review of basic clinical parameters. It's expected that the heart rate and respiratory rate may be elevated, while the rectal temperature generally remains within the normal range [32]. During the visual examination, signs like excessive salivation, possible erythema of the lips, swelling of lips and tongue, oral ulcers, and audible inspiratory stridor may be observed [32]. Additional symptoms may include stomatitis, laryngitis, and glossitis [127], along with gastrointestinal issues like vomiting, diarrhea, abdominal pain, and drooling [128].

Applying diagnostic imaging methods to reveal oxalate toxicosis, lateral X-rays [32] or ultrasound examinations can shed light on the stomach that may appear dilated with both gaseous and fluid content due to the emetic and diarrheal conditions. The intestinal wall could also show alterations, while the jejunum and ileum can be shortened as a result of enteritis. The mesenteric lymph nodes may appear enlarged also referred to as lymphadenomegaly due to the inflammation of gastric mucosa [85]. X-rays might also reveal a mild alveolar pattern in the left cranial and cranial portion of the left caudal lung lobe, which is indicative of aspiration pneumonia [32]. Ethylene glycol poisoning can lead to the formation of "hempseed"-shaped calcium oxalate crystals, described by Ramesh [1]. The presence of such crystals can be a proof of oxalate poisoning after the consumption of oxalate crystal-forming plants. Ethylene glycol poisoning can also be characterized by an increase of renal cortical

and medullary regions on ultrasound pictures [109, 129]. An endoscopic diagnosis can reveal gastric ulceration and the presence of plant materials in the stomach [7].

Concerning other diagnostic methods to detect oxalate intoxication, crystalline keratopathy (development of oxalate crystals in the corneal epithelium of eyes) can be detected using a slit-lamp biomicroscope [130]. A simple method, as palpating the tongue can be crucial, as well. Rigidity might suggest a primary muscular issue affecting saliva clearance. Measuring creatine kinase levels in blood can also be important because elevated creatine kinase levels often indicate muscle fiber lesions [131, 132]. A particularly significant marker for detecting plant oxalate poisoning is an unusually high ratio of creatinine compared to BUN (Blood Urea Nitrogen) [37, 133]. Within 3 to 6 hours after ingestion, calcium oxalate crystals can be detected in urine [127, 134].

Laboratory tests can reveal isosthenuria, a condition where urine has a specific gravity similar to that of plasma, indicating a loss of concentrating ability in the kidneys [1, 129]. Furthermore, hypoosmolality (a lower than normal concentration of solutes in the blood, which can indicate conditions such as overhydration), high osmolar gap (a discrepancy between measured osmolality and calculated osmolality, suggesting the presence of unmeasured solutes), high anion gap (an increase in the difference between measured cations and anions in the blood, indicating metabolic acidosis), normochloremic metabolic acidosis (a type of metabolic acidosis characterized by a normal serum chloride level), prerenal azotemia (an increase in nitrogenous waste products in the blood due to inadequate blood flow to the kidneys) and renal azotemia (an elevation of blood urea nitrogen and creatinine due to intrinsic kidney damage), and hyperkalemia (an elevated level of potassium in the blood) are typical laboratory results found in animals poisoned with oxalate-rich plants [32, 129].

The prognosis is generally considered to be good to favorable when the treatment is administered promptly after the ingestion of oxalate-producing plants. If the veterinarian initiates treatment within a short period of time following exposure and promptly diagnoses plant-originated oxalate poisoning, the likelihood of a positive outcome significantly increases. The early intervention is crucial, as it allows for more effective management of the poisoning and reduces the risk of severe complications [7, 32, 37, 85, 135].

4.8. Treatment of oxalate toxicosis

4.8.1. Historical versus current perspectives

Historical treatments for oxalate poisoning focused on promoting urinary oxalate excretion and crystal formation. The discovery of *Oxalobacter formigenes* in 1985 [65] led to a significant breakthrough, reducing the risk of renal stones by 70% [136]. This bacterium, when combined with antibiotics like cephalosporins or vancomycin, enhances the effectiveness of treatments, as it is resistant to certain antibiotics [137]. Research with guinea pigs revealed that secondary bile salts could help reducing oxalate levels in the cecum, suggesting a link between hyperoxaluria and bile salt malabsorption [138].

Current treatments for calcium oxalate bladder stones in pets include surgical and several non-surgical techniques as shown in **Table 5**.

Table 5. Surgical and non-surgical techniques for treating Ca-oxalate bladder stones in pets.

Technique	Description	References
Intracorporeal laser lithotripsy	This method uses a laser light to fragment stones within the bladder or urethra, with larger pieces removed using a basket and smaller fragments flushed out.	[139]
Electrohydraulic lithotripsy	An electrode generates electric sparks in saline solution to break stones. The resulting fragments are then removed similarly to laser lithotripsy.	[140]
Extracorporeal shockwave lithotripsy	Shock waves, applied externally through water or a cushion, fragment stones, which are then guided out using imaging techniques.	[141]
Ultrasonic lithotripsy	High-frequency ultrasound waves break stones into small particles, which are then flushed out. Larger pieces can be extracted using forceps or baskets.	[142]
Surgical removal	For large or numerous stones, surgical options like percutaneous cystolithotomy or cystotomy may be necessary, particularly in small male dogs and most male cats where minimally invasive techniques are impractical. Endoscopic nephrolithotomy and ureterotomy are also considered for complex cases.	[143, 144]

For the treatment of acute oxalate poisoning in horse, usually symptomatic treatment options are applied. Intravenous calcium supplementation containing calcium borogluconate, magnesium hypophosphite, phosphorus, and glucose are usually recommended in cases when

neuromuscular excitation was observed. Calcium carbonate and DCP (dicalcium phosphate) in rations of 1:1 or 1:2 are administered orally for long term to treat or prevent hypocalcaemia after oxalate intoxication [75]. If oxalate crystals are present in the stomach, activated charcoal acting as an absorbent is given orally.

4.8.2. Conventional medicine

When managing a case of poisoning with oxalate-containing plants in pets, a comprehensive and systematic approach is essential to ensure effective treatment and recovery.

The first critical step is to initiate fluid therapy to rehydrate the patient and prevent the onset of anuric renal failure. This should be started within the first 24 hours after oxalate-containing plants were ingested. Physiological saline (0.9% NaCl) solution should be administered intravenously at a rate of 200 ml/hour [85]. This fluid diuresis must be maintained for 24 to 72 hours. If anuric renal failure occurs, more invasive treatments, such as peritoneal or haemodialysis may be required [37]. Diuretics, like furosemide, given at a dosage of 1–3 mg/kg bw, proved to be powerful in treatment of *Dieffenbachia* poisoning [85].

To address the poisoning, induction of vomiting should be done as soon as possible to remove stomach contents. Even after repeated vomiting, gastric lavage is recommended to remove toxins from stomach ridges. For dogs, emetic drugs such as apomorphine and xylazine are recommended [145]. For cats, dexmedetomidine and xylazine are preferred [146]. After inducing vomiting, administer activated charcoal to help absorb any remaining toxins in the gastrointestinal tract [37].

Supportive care is crucial for managing symptoms and aiding recovery. Administer antiemetic drugs like ondansetron (0.1–1 mg/kg bw), and antimicrobial agents, such as metronidazole (15–25 mg/kg bw) to prevent potential infections. Gastric protectants like omeprazole (0.5 mg/kg bw) should also be given. Probiotics (2 g, orally) can help maintain gut health, while Dexa-cytoneurim NFF^{TM}, which is a combination of dexamethasone and vitamin B, supports overall recovery. Additionally, Aminomix Gold, a nutritional supplement for parenteral nutrition, should be administered at 0.5 g/kg bw. Physiotherapy should be integrated into the treatment plan to stimulate muscle movements and recovery [85].

In some cases, endoscopic removal of gastric contents may be necessary to further address the poisoning. For this procedure, hydromorphone (0.1 mg/kg bw) should be administered for analgesia, followed by ketamine (5 mg/kg bw) and midazolam (0.5 mg/kg bw) for inducing anaesthesia. To maintain intravascular volume during anaesthesia, hetastarch

(1 ml/kg bw/h) can be used. If there is a suspected allergic reaction causing airway obstruction, dexamethasone (2.5 mg/kg bw) and diphenhydramine (2.5 mg/kg bw) are appropriate. To treat respiratory distress syndrome, acepromazine (0.025 mg/kg bw) can be administered. In severe situations, involving asphyxia, a temporary tracheostomy might be required [32].

For patients experiencing hypocalcaemia, intravenous Ca^{2+} should be administered. Oral supplements like lime water, milk, or calcium lactate can also be beneficial [8]. If convulsions are present, monitoring plasma calcium levels is important, and treatment with borogluconate may be considered. Liver protectants such as S-Adenosylmethionine (SAMe), N-Acetylcystein (NAC), and silymarin can support liver function during recovery [85, 147].

A comprehensive treatment strategy that addresses both the acute symptoms and long-term recovery is crucial to cure oxalate poisoning. A tailored combination of treatments and interventions (applying personalized medicine) for each specific case can significantly enhance the likelihood of a successful recovery.

4.8.3. Alternative medicine

Phytotherapy and homeopathy represent two distinct groups of methodologies within alternative medicine, each characterized by its unique principles, mechanism of actions, and supporting evidences.

4.8.3.1. Phytotherapy

Phytotherapy, or herbal medicine, made significant strides during World War II when various plant extracts were started to be used in treating both domestic and farm animals in conventional veterinary practice. This approach has gained popularity among farmers due to the increasing emphasis on sustainable livestock management [148]. Phytotherapy relies on the active compounds found in plants, with its practices backed by empirical evidence and scientific research demonstrating the medicinal benefits of these substances [149]. These herbal products are typically regulated as either dietary supplements or drugs, depending on their intended use and claims. Regulatory bodies such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) establish guidelines to ensure their safety and effectiveness [150].

Research verifies phytotherapeutic treatments to alleviate symptoms and prevent, more rarely cure diseases, which makes it understandable why their usage is widely spread in ethnoveterinary medicines till present [148].

In Europe, the concept of phytotherapy was introduced by a French physician, Henri Leclerc, in 1913. His famous book [151] contains the basics of European herbal medicine. Leclerc's work helped to establish phytotherapy as a recognized field of study and practice in Europe. The publication of his book marked a significant milestone in the development and acceptance of plant-based therapies on the continent.

In the traditional Asian medicine, the Japanese Kampo medicine and Chinese herbal medicine could be mentioned. In the Japanese Kampo medicine, *Alisma orientale*, also known as takusha, plays a significant role in preventing calcium oxalate stone formation in humans. It inhibits the aggregation of calcium oxalate crystals, as demonstrated by Koide et al. [152]. Chinese herbal medicine includes wuling san wan, a traditional remedy made of five fungal and herbals components: "poria cocos" (the sclerotium of a wood-inhabiting fungus, *Wolfiporia extensa*) and the sclerotium of another wood-decaying fungus ("polyporus"), *Polyporus umbellatus*, currently *Cladomeris umbellata*. It also contains "rhizoma atractylodis macrocephalae" (the rhizome of *Atractylodes macrocephala*, a medicinal plant in China), "rhizoma alismatis" (the rhizome of *Alisma plantago-aquatica*, an aquatic plant), and "ramulus (cortex) cinnamomi" (the inner bark of the plant *Cinnamomum verum*). This formulation is known for its ability to inhibit calcium oxalate crystallization by affecting both the nucleation and aggregation stages of crystal formation, as outlined by Tsai et al. [153].

The Indian and Ayurvedic Medicine, applied for humans, deals with the plants, *Ammannia baccifera*, *Tribulus terrestris*, *Crataeva nurvala*, and *Dolichos biflorus*. In Indian medicine, *Ammannia baccifera* is utilized for protection against the formation of calculogenic materials. It helps dissolve pre-formed calculi and increases the urinary excretion of calcium, magnesium, and oxalates, leading to a decrease in blood urea nitrogen levels [154]. *Tribulus terrestris* is another important herb in Indian medicine, specifically used to prevent the formation of urinary stones, as indicated by Anand et al. [155]. *Crataeva nurvala* is known for its efficacy in dissolving calculi and reducing blood urea nitrogen levels, contributing to its role in stone management [156]. The Ayurvedic herb *Dolichos biflorus* is recognized for its ability to impede the formation and growth of urinary stones, providing a beneficial alternative in stone treatment [157].

In other regions, *Herniaria hirsuta* is notable for its effects on calcium oxalate stones. It promotes the formation of Ca-oxalate raphide crystals, increases the number of stones while

reducing their size, and prevents crystal binding to renal cells, as reported by Butterweck & Khan [158]. *Phyllanthus niruri*, used in Brazilian folk medicine, is effective in interfering with the early stages of calculi formation. It is applied both for treatment and prevention of urinary stones [159].

Lemon juice, available in 100% or 75% concentrations, has been shown to be powerful against stone formation in rats. However, it is unsuitable for pets due to its toxic effects on both cats and dogs [160].

Table 6 provides an overview of herbal taxa and plant products for the prevention of the formation of Ca-oxalate crystals in pets and phytotherapeutic treatments.

Table 6. An overview of medicinal plant species and products used in phytotherapy for Ca-oxalate stone treatment.

Effect type	**Medicinal plant species/products and their specific effects**
Common effects on calculi formation	*Ammannia baccifera* prevents calculi formation and increase urinary excretion, making it beneficial for overall urinary health [154].
	Tribulus terrestris shares a similar role in preventing stone formation, indicating its effectiveness in urinary tract support [155].
	Crataeva nurvala not only dissolves calculi but also decreases blood urea nitrogen (BUN) levels, highlighting its dual action in both stone management and renal function improvement [156].
Specific effects on Ca-oxalate stones	*Alisma orientale* specifically prevents Ca-oxalate stone formation and inhibits aggregation, suggesting its targeted application in managing this type of urinary stone [152].
	Wuling san wan works by inhibiting Ca-oxalate crystallization through effects on nucleation and aggregation, reinforcing its role in the prevention of these stones [153].
	Herniaria hirsuta encourages the formation of Ca-oxalate raphides and reduces stone size, indicating a unique approach to manage existing stones rather than solely preventing their formation [158].
	Dolichos biflorus impedes both, stone formation and growth [157].
Early intervention in stone formation	*Phyllanthus niruri* interferes with early stone formation, making it particularly useful for individuals at risk of developing urinary stones [159].
	Lemon juice protects against stone formation [160].

4.8.3.2. Homeopathic therapy

Homeopathy, developed by Samuel Hahnemann, is founded on the principle of "like cures like" and applies remedies that are diluted to extremely low concentrations. This theory suggests that such dilutions retain a "memory" of the original substance, a concept that lacks

robust empirical validation [161]. Homeopathic remedies are less strictly regulated and are often sold as over-the-counter products, with their effectiveness largely attributed to placebo effects [162]. The core mechanism of homeopathy involves the idea of extreme dilution and the supposed "memory" of substances used [163].

This chapter examines homeopathic approaches to manage and prevent urolithiasis (the formation of crystals in the urinary system) highlighting specific plant species and their therapeutic effects. Urolithiasis can occur after the consumption of oxalate-containing plants. This significant health issue is typically managed with both non-surgical and surgical methods but none of them can prevent the formation of new stones.

For example, *Berberis vulgaris*, commonly known as “berberry”, is a plant species from the Berberidaceae family widely used in homeopathic therapies for treating various renal illnesses, especially to remove kidney stones. A study showed that the extract of the root bark of *B. vulgaris* is preferred over the crude extract in curing nephrolithiasis [164]. The crude aqueous–methanol extract of root bark contains constituents that can protect against changes associated with oxidative stress, impairment of renal function, oxidative damage to kidney and biochemical changes in urine composition. Therefore, it prevents the formation of uroliths through the inhibition of Ca-oxalate crystallization [165]. These effects can be explained by the strong antioxidant activity of *B. vulgaris*. The homeopathic preparation of *B. vulgaris* root bark can promote an increase in the activity of antioxidant enzymes like superoxide dismutases (SODs), catalases (CATs), the glutathione peroxidase (GPx) and glutathione reductase (GR) [166], but can also enhance the work of glucose-6-phosphate dehydrogenase enzyme complex (G6PD) with pivotal roles in glycolysis and the biosynthesis of the most important reducing powers, the NADH and NADPH. Evidently, it can also help non-enzymatic antioxidants, such as tocopherol (vitamin E), glutathione (GST), and ascorbic acid (vitamin C), which makes this agent effective in alleviating the harmful effects of oxidative stress on tissues [167, 168].

Another notable remedy can be extracted from *Lycopodium clavatum*, which has been used successfully in treating ureteric stones, as demonstrated by Hati et al. [169]. Sumreen et al. [170] demonstrate that *Berberis vulgaris* and *Lycopodium clavatum* can serve as effective alternatives to surgery for treating nephrolithiasis, even for stones larger than 8 mm, which is typically considered as a threshold for surgical intervention.

Less known homeopathic plant species reported to have anti-urolithic effects include: *Ammonium phosphoricum*, *Arundo mauritanica*, *Asparagus officinalis*, *Balsamum peruvianum*, *Chenopodium anthelminticum*, *Chimaphila umbellate*, *Calcare arenalis*,

Chininum sulphuricum, *Coccus cacti*, *Eleutherococcus senticosus*, *Epigea repens*, *Fabiana imbricata*, *Galium aparine*, *Hydrangea arborescens*, *Ocimum canum*, *Solidago virgaurea*, *Stillingia sylvatica*, and *Stigmata maydis* [171].

4.8.4. Dietary treatment

Research indicates that the formation of Ca-oxalate uroliths increased by approximately 26% in dogs and by 23% in cats between 1981 and 2007 [172]. Diets that reduce urine acidity and contain sufficient magnesium were reported to decrease the risk of the formation of Ca-oxalate stones [173, 174]. However, such forages can increase the likelihood of struvite stones in cats [175]. Diets with high water and protein contents but containing a moderate level of magnesium, phosphorus, and calcium are associated with a reduced risk of Ca-oxalate urolith formation [173, 175]. Similarly, dry diets formulated with carefully balanced concentrations of protein, calcium, phosphorus, magnesium, sodium, potassium, and chloride may help minimize Ca-oxalate urolith formation [176]. Additionally, the occurrence of hyperlipidaemia in dogs suggests a link between hypertriglyceridemia (HTG) and the formation of Ca-oxalate uroliths in the lower urinary tract, indicating that low-fat diets should be recommended for animals after oxalate poisoning to reduce the risk of stone formation [166, 176, 177].

To prevent calcium oxalate stone formation and manage complications, several approaches are recommended. First, restricting dietary calcium to between 0.3% and 0.6% dry matter (DM) can help minimize excessive calcium absorption and excretion. It is also important to avoid supplements of vitamins C and D, as these can increase intestinal calcium absorption and contribute to oxalate formation [178]. In contrast, Thiamine (vitamin B1) and Pyridoxine (vitamin B6) have been identified for their ability to reduce oxalic acid formation and oxalate deposition [179, 180]. Additionally, applying soothing agents like milk, egg whites, and aluminum hydroxide can alleviate gastric discomfort, especially since lipid levels in food can enhance the absorption of fat-soluble toxins [181]. For severe poisoning cases, antibiotic treatment is advised to lower the risk of sepsis [182]. Presently, several commercially available diets, such as Hill's u/d diet, Waltham S/O Lower Urinary Tract Support, Medi-Cal Reduced Protein, and Veterinary Medical Diets, are designed to support treatment [114, 178].

A diet rich in antioxidants has been shown to reduce the incidences of stone formation [183]. Liver protectants such as S-Adenosylmethionine (SAMe), N-Acetylcysteine (NAC), and silymarin can aid liver function during recovery from intoxication [85, 147]. Studies

reveal that sheep consuming grass not treated with calcium fertilizers had lower blood calcium levels (12.5 mg/dl) compared to those fed calcium-fertilized grass (13.4 mg/dl). This suggests that avoiding calcium-fertilized grass in diet can help counteracting the negative effects of oxalates. Integrating plants and herbs that are low in oxalates can aid in preventing toxicity. Soaking and straining the hay can effectively reduce its oxalate content [184].

4.9. Prevention of oxalate toxicosis

Encouraging dietary management can help inhibit and prevent Ca-oxalate stone formation following intoxication or consumption of oxalate-rich plants. Owners should take an extra care of the potential toxicity of plant species and strive to keep them out of pastures and households. It is imperative to recognize that canines experiencing boredom are more prone to chew ornamental plants [85]. Felines unable to consume grasses are more inclined to eat exotic, often toxic ornamental plants [68]. Addressing these behaviours requires a holistic approach, including a varied diet and a continuous access to non-toxic plant species. Increasing awareness among pet owners about these risks can help protect their animals from accidental poisonings.

5. Discussion

Oxalate crystal-related pathological conditions principally occur due to the consumption of plants rich in oxalate crystals. The current increase in such cases pose substantial hazards to animals. Consumption of oxalate-rich plants may lead to poisoning in pets and food-producing animals, which can manifest in different forms, including peracute, acute, and chronic toxicosis. The manifestations of oxalate toxicosis are diverse both among species and individuals, in which dietary habits, species identity, and the chemical composition of foods and forages providing oxalate crystals influence the clinical signs [1, 64, 65]. Understanding these variations is critical, as monogastric animals, such as carnivores and equids, are less tolerant to the effects of oxalate crystals compared to ruminants, which possess oxalate-degrading bacteria in their rumen [8].

Toxicokinetics of oxalate crystals include absorption through mucous membranes, rapid distribution in blood circulation, and excretion via urine. The acute oxalic acid toxicosis is the most commonly observed form of this condition, that often leads to hypocalcaemia, neuromuscular symptoms, and potentially, organ damages in various species [73, 74]. Peracute oxalic acid toxicosis manifests rapidly after exposure to oxalate-rich plants causing severe oral irritation and a range of distressing clinical symptoms in the affected animals [7, 25, 32, 72]. Chronic oxalate toxicosis, which develops over months or years, can result in serious health issues such as electrolyte imbalances, bone developmental or metabolic disorders like osteodystrophia fibrosa in horse, and the formation of nephroliths or uroliths in pets [14, 86]. There is a limited knowledge regarding the detailed mechanism of action of oxalate crystals including the formation of crystals in blood vessels and the urogenital system, that may lead to vascular damages (blockages), mineral deficiencies, and local inflammation [14, 98]. Further investigation is needed to characterize these mechanisms and the long-term consequences of oxalic acid intoxication in pets.

In contrast, ethylene glycol poisoning has been studied in far greater detail than plant-derived oxalate intoxication. Dogs are more frequently affected by ethylene glycol due to their preference of its sweet taste. Cats are less frequently affected due to their different taste preferences but can ingest some ethylene glycol from their fur through grooming [107, 110].

Treatment of oxalate poisoning needs a comprehensive and systematic approach involving fluid therapy, emesis induction together with supportive care [85]. Early diagnosis

through physical examinations, imaging, and laboratory tests are critical for a favourable prognosis like the promptly applied treatment [7, 32, 37]. Conventional medical treatments should be prioritized, alternative treatments, such as homeopathic and phytotherapeutic options are also available. For example, phytotherapy applies certain fruit juices and plant extracts that can help reducing the amounts and enhancing the excretion of calcium oxalate crystals. Also, plant juices are often powerful against the formation of urinary calculi [158], however, their actual mechanism of action remains speculative and require further research. Dietary treatments that reduce urine acidity and balance minerals may prevent calcium oxalate urolith formation in pets, though limited data on the various diets of animal species complicates broader recommendations [172, 173, 183].

Preventing oxalic acid toxicosis necessitates a multifaceted strategy that involves dietary management and the education of pet owners about the risks associated with toxic plants, including *Dieffenbachia* species and other members of family Araceae. These herbal species are among the most common causes of plant oxalate intoxications in pets worldwide [7, 30]. However, cases of oxalate poisoning from household plants are rarely reported in small animal practice, the frequently applied ornamental, mainly aracean, oxalate-rich plant taxa in flats highlight the need for greater owner awareness. The performance of oxalate crystals at different developmental stages during animal growth is still poorly understood representing an important field for further research. Filling these knowledge gaps through targeted research and educational initiatives can help protect pets from the harmful effects of oxalate-rich plants and enhance overall health outcomes.

6. Conclusions

I reviewed scientific papers and books (184 in total) published in the last 70 years about oxalate toxicosis in pets and livestock. The vast majority of papers focused on case studies dealing with livestock animals (cattle and sheep) but only some outlined oxalate toxicosis in pets (cats and dogs) from plant sources. Much information was available on the conventional treatments, but much less for the alternative ones. Ethylene glycol poisoning and its conventional treatment options had a wide literature focusing on pets, but I found much less information about the treatment of plant-derived oxalate intoxications. Many studies detailed the clinical signs and pathological changes associated with oxalate poisoning, yet there was a limited exploration of long-term management and prevention strategies. There is an emerging need for comprehensive reviews that summarize modern treatment methods and compare traditional approaches with newer alternatives. Future research should put more focus on the alternative treatments such as phytotherapy and homeopathy, which are promising in alleviating symptoms and preventing intoxications according to preliminary studies.

Traditional treatments for oxalate poisoning focus on managing symptoms with fluid therapy, calcium supplements, and decontamination techniques. Alternative treatments like phytotherapy and homeopathy are emerging as useful adjuncts. Phytotherapy uses plant-based treatments to prevent the formation of stones, while homeopathy provides remedies that help maintain renal health, especially highlighting the plant species, *Berberis vulgaris*, for its effectiveness in removing kidney stones. However, both phytotherapy and homeopathy are not extensively studied, and their effectiveness is largely attributed to placebo effects. Despite this, these methods can complement traditional treatments, potentially reducing the need for invasive procedures.

Common sources of oxalate toxicity include certain, mostly ornamental plant taxa and household chemicals. Members of the aracean plant genera like *Dieffenbachia* and *Philodendron*, are frequently applied species in flats. The widely used antifreeze, ethylene glycol, can also be a significant source of oxalate intoxication due to its fast conversion to oxalic acid in the body. Awareness and management of these sources are key to preventing poisoning.

Diagnosing oxalate poisoning involves clinical examinations, laboratory tests, and imaging. Symptoms include salivation, oral ulcers, and gastrointestinal issues. Laboratory

tests for blood calcium and urine oxalate levels, along with X-rays and ultrasounds, can confirm the diagnosis. Preventive measures include diet management, hydration, and avoiding oxalate-rich plants and chemicals.

Tolerance to the formation of oxalate crystals varies by species. Ruminants like cattle have higher tolerance due to oxalate-degrading bacteria in their rumen. Pets like dogs are more prone to oxalate poisoning, especially small breeds. Cats are less likely to consume oxalate-rich plants but some breeds are genetically predisposed to the development of oxalate stones. Preventive strategies should consider these differences.

A varied diet helps to prevent oxalate crystal formation by maintaining a diverse gut microbiota, which helps breaking down oxalate ions and their salts in the guts. This, combined with homeopathic approaches that support gut health, can prevent the development of metabolic diseases and reduce the risk of oxalate poisoning. Integrating dietary management with alternative treatments can offer a comprehensive approach to managing oxalate toxicosis.

7. Summary

This work deals with the causes of oxalate poisoning in animals, examining specific plant species (members of family Araceae) and other sources of oxalate ions such as ethylene glycol, which can seriously affect both pets and food-producing animals. I examined the symptoms of oxalate poisoning, which can appear suddenly, develop quickly, or take a long time to manifest depending on the animal species, diet, and the type of oxalate crystals involved. I collected and classified diagnostic options of oxalate intoxication and compared conventional treatments with alternative methods like homeopathy and phytotherapy.

The study reveals that monogastric animals, like carnivores or horse, are more prone to oxalate poisoning compared to ruminants, which usually have a specific bacterial community in their rumen that can break down the oxalate ion or its crystals. Key symptoms of oxalate poisoning include hypocalcaemia, neuromuscular or circulatory issues leading to organ damages. Acute cases often present with sudden symptoms such as salivation, while chronic exposure can lead to serious health problems like electrolyte imbalances, bone developmental and metabolic disorders (such as osteodystrophia fibrosa in horse), and the formation of kidney stones. Oxalate toxicokinetics include absorption through mucous membranes, rapid distribution in blood circulation and excretion via urine.

Treating oxalate poisoning requires a comprehensive approach, including fluid therapy, inducing vomiting, and supportive care. Early diagnosis using physical examinations, imaging, and laboratory tests is crucial for a good prognosis. While conventional treatments are prioritized, alternative therapies, like homeopathy and phytotherapy are also being explored. Some fruit juices and plant extracts might help enhancing calcium oxalate excretion and prevent the formation of urinary stones, though more research is needed to understand their effectiveness. Preventive strategies include the management of the animal's diet and the education of pet owners about the potential threats of oxalate-producing plants.

Looking ahead, more research is needed to understand the long-term effects of oxalate exposure, the exact mechanism and requirements of oxalate crystal formation in blood vessels and tissues, and the details how the presence of oxalate ions affect animals at different stages of development. Widening the knowledge of pet owners in these areas along with targeted educational efforts can help protecting pets and livestock animals from the potential threats of oxalate sources (certain plant species and chemicals).

8. References

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Thesis progress report for veterinary students

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Thesis title: Oxalate Toxicoses in Pets: a Comparison of Conventional and Alternative Medicine

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2024	04	11	finding a topic suitable for the student (Teams meeting)	
2.	2024	05	07	collecting and sharing literature (Teams meeting)	
3.	2024	05	14	collecting and sharing literature	
4.	2024	06	10	sorting pieces of literature into the main chapters of thesis draft	

Grade achieved at the end of the first semester: 5

Consultation– 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2024	09	30	formation of main chapters of thesis	
2.	2024	10	27	rewording and restructuring the thesis draft	
3.	2024	10	29	correcting sentences to make the thesis text more scientific	
4.	2024	11	09	finalizing sentences in thesis draft	
5.	2024	11	19	final editing and typesetting of thesis file	

Grade achieved at the end of the second semester: 5

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....
signature of the supervisor

Signature of the student: ...Kamarovska.....

Signature of the secretary of the department: .....

Date of handing the thesis in 29.11.2024.

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