

REVIEW ARTICLE

Epithelial barrier dysfunction and associated diseases in companion animals: Differences and similarities between humans and animals and research needs

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Abstract

Since the 1960s, more than 350,000 new chemicals have been introduced into the lives of humans and domestic animals. Many of them have become part of modern life and some are affecting nature as pollutants. Yet, our comprehension of their potential health risks for both humans and animals remains partial. The “epithelial barrier theory” suggests that genetic predisposition and exposure to diverse factors damaging the epithelial barriers contribute to the emergence of allergic and autoimmune conditions. Impaired epithelial barriers, microbial dysbiosis, and tissue inflammation have been observed in a high number of mucosal inflammatory, autoimmune and neuropsychiatric diseases, many of which showed increased prevalence in the last decades. Pets, especially cats and dogs, share living spaces with humans and are

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exposed to household cleaners, personal care products, air pollutants, and microplastics. The utilisation of cosmetic products and food additives for pets is on the rise, unfortunately, accompanied by less rigorous safety regulations than those governing human products. In this review, we explore the implications of disruptions in epithelial barriers on the well-being of companion animals, drawing comparisons with humans, and endeavour to elucidate the spectrum of diseases that afflict them. In addition, future research areas with the interconnectedness of human, animal, and environmental well-being are highlighted in line with the "One Health" concept.

KEYWORDS

companion animals, epigenetics, epithelial barrier, exposome, microbiota, skin

1 | INTRODUCTION

The role of companion animals, especially dogs and cats, in human society has changed in the last century, and recently, they are considered not only moral subjects, but even integral family members with a deep affective bond with their human partners. In 2021, the number of dogs in European households was estimated to be around 72.7 million, while cats were even more popular, with a total of 83.6 million.¹ Conspicuously, a multitude of elements to which people are exposed due to modernization and urbanization can directly impact animals as well. Cats and dogs share living spaces with humans, even sleeping quarters in some households. This proximity means that substances utilized for household or laundry cleaning inevitably come into direct contact with these animals. Therefore, household cleaners and personal care products used by humans can also affect animal health. There is also a noticeable uptick in the utilization of cosmetic products specifically designed for animals. Furthermore, animals residing in urban areas are subject to the impacts of air pollution and micro- and nano-plastics to a similar extent as humans.

The epithelial barrier theory (Box 1) is a comprehensive explanation for the worldwide surge in chronic noncommunicable health conditions reaching epidemic proportions over the past 65 years.²⁻⁴ The origins of this theory date back to the early 20th-century, when immune-mediated damage to the epithelial barrier in chronic allergic inflammation. Early findings revealed that T cells infiltrating the skin could induce keratinocyte apoptosis, leading to eczema and a weakened skin barrier.⁵⁻⁸ This concept has since been broadened to include barrier damage mediated by type 2 immunity in various conditions, ranging from chronic autoimmune diseases to neurodegenerative and psychiatric disorders.^{3,9-12} In this context, conditions that arise or worsen due to an impaired epithelial barrier can be categorized into three main groups. The first group includes chronic diseases characterized by localized barrier defects, leading to pathology in affected skin and mucosal tissues, as seen in allergic diseases, inflammatory bowel disease, and coeliac disease.¹³ The second group encompasses chronic autoimmune and metabolic disorders where compromised barriers and microbial dysbiosis in the gut contribute to the initiation and progression of diseases such as type 1 and type 2 diabetes, obesity, rheumatoid arthritis, multiple sclerosis, ankylosing

BOX 1 Key points on the early understanding of "Epithelial Barriers"

- The origins of the epithelial barrier theory can be traced back to research conducted at the start of the century, which revealed immune-mediated damage to the epithelial barriers in cases of chronic allergic inflammation in the skin and lungs.⁵⁻⁸
- Among the earliest discoveries related to immune-mediated damage to the epithelial barrier, one of the key observations was made in individuals with atopic dermatitis and allergic contact dermatitis. T cells infiltrating the skin could trigger keratinocyte apoptosis, resulting in the development of eczema and a compromised skin barrier.⁵⁻⁸
- In asthmatic airways, basement membrane thickening and IgA secretion form a barrier that has "keep away" effect. Opening the epithelial barrier allows inflammatory cells to migrate, aided by mucus production, coughing, ciliary movement, and the death of highly activated epithelial cells, which collectively expresses "wash away" effect to reduce the inflammation.³¹²
- Numerous investigations have expanded upon the notion of barrier damage mediated by type 2 immunity in a wide variety of diseases from chronic autoimmune disorders to neurodegenerative or psychiatric conditions.³
- Disruptions in the integrity and function of the epithelial barrier can lead to increased permeability, allowing the penetration of foreign substances, including allergens, microbes, toxins and pollutants and triggering inappropriate immune responses.⁷⁷
- The epithelial barrier theory incorporates a wide range of multidisciplinary perspectives, combining the collective knowledge amassed on this subject to date while considering past hypotheses. It presents an overarching concept that also embraces previous views from the Hygiene, Old Friends, and Biodiversity hypotheses.^{3,9,10}

spondylitis, hepatitis, and systemic lupus erythematosus. The third group consists of chronic conditions where defects in the gut barrier and microbial translocation are linked to neurodegenerative or psychiatric disorders, including autism spectrum disorder, chronic depression, stress-related psychiatric conditions, Parkinson's disease, and Alzheimer's disease.^{3,9,13,14} Epithelial Barrier Theory was built upon these ideas, suggesting that environmental changes due to industrialization, urbanization, and Western lifestyles have affected epithelial barriers in the skin, airways, and gut, thereby increasing permeability and triggering immune responses.³ The epithelial barrier theory integrates multidisciplinary insights and past hypotheses, providing a framework for understanding the pathophysiology of diseases associated with barrier dysfunction and guiding new approaches to diagnosis, treatment, and prevention (Box 1). The prevalence of allergic diseases and autoimmune conditions such as asthma, allergic rhinitis, atopic dermatitis (AD), inflammatory bowel disease (IBD), eosinophilic esophagitis, drug-induced anaphylaxis, food allergy, diabetes, rheumatoid arthritis, multiple sclerosis, and celiac disease has become a significant global health issue, reaching even epidemic levels. This sharp increase indicates that environmental factors and climate change adversely affect the immune system.^{3,4,15–17} Studies have pointed out a progressive escalation, such as the prevalence of specific IgG and IgE in reactions to particular allergens.^{3,18–21} Notably, nearly all infants tested at the age of 1 year showed the presence of milk-specific and egg-specific IgG antibodies in 2018.²⁰ The prevalence of allergen-specific IgE (to any allergen) exceeds 50% of the population in Europe, Northern America, and Australia.³ The ambiguity surrounding the epidemiological status in animals can be attributed to the absence of comprehensive studies, in contrast to the extensive research conducted in human populations.

The well-being of humans, animals, and the environment is interconnected, as acknowledged by the One Health Initiative of the World Health Organization (WHO).²² Companion animals and humans residing in middle- and high-income nations experience similar non-communicable diseases.^{22,23} In this context, dysfunction of the epithelial barriers can lead to various health issues not only in humans but also in different animal species. Given the extensive use of food additives, cleaning and personal care products, disinfectants, cleaning sprays, and various chemicals for companion animals, it can be postulated that the dynamics in animals closely parallel those in humans, taking into consideration the principles of the epithelial barrier theory. This approach addresses these issues in a multidisciplinary way, emphasizing the interconnectivity between human, animal, and environmental health. Coinciding with the "Westernization" of the human diet, which includes high consumption of ultra-processed foods rich in fats, sugars, and salts,²⁴ a similar shift has been seen in dog feeding methods in Western countries towards processed foods, high in carbohydrates, such as kibbles.²⁵ This dietary trend contrasts sharply with dogs' evolutionary adaptations, which are primarily geared towards consuming animal proteins and fats.²⁶ In this regard, dogs do not have any nutritional requirement for carbohydrates and typically show a preference for their ancestral diet. Crucially, the composition of the gut microbiota is strongly

influenced by these dietary choices.²⁷ Moreover, the Westernized lifestyle is closely linked to the introduction of numerous chemicals into the daily lives, increased stress, decreased physical activity, shifting away from natural settings, and being confined to indoor environments²⁴ for not only humans but also domestic animals.

It is important to note that there is a dearth of substantiating data, and ample evidence suggesting that testing procedures are insufficient, lacking precision, and may raise ethical concerns, even if some official agencies from various countries provide assurances regarding safety in animals. Current technology and detection methods in veterinary medicine generally lag behind those in human medicine. Additionally, the prohibition, restrictions, and legal and regulatory oversight of many chemicals are often insufficient in most countries. There is no detailed and comprehensive study on companion animal health through the lens of the epithelial barrier theory. Therefore, the objective of this comprehensive paper is to demonstrate the applicability of similar conditions in companion animals, encompassing the fundamental mechanisms behind epithelial barrier disruptions that contribute to various infectious, metabolic, and immunological diseases of animals. In this context, we focused on the environmental changes over the past decades that have led to an increase in epithelial barrier insults, not only for humans but also for domesticated species, particularly companion animals. We have thoroughly and comparatively discussed the potential effects that could lead to these conditions.

2 | THE EPITHELIAL BARRIERS IN HUMAN AND ANIMALS

The epithelial barriers of the skin and mucosa play a crucial role in protecting the organism against the external environment by acting as a physical, chemical and immunological barrier. They serve as the first line of defense against external pathogen invasion or foreign substance infiltration to preserve the body's structural and functional integrity and maintain homeostasis within the body.^{14,28} The structure of the epithelium and its functions vary among the skin, gastrointestinal system, and respiratory tract.^{11,29,30} The skin barrier is a strong, stratified, and multicellular defense mechanism. It consists of the *stratum corneum*, which provides physical thickness and strength. The intercellular lamellar lipid and protein complexes within the skin barrier play a crucial role in maintaining its integrity.^{11,31} The respiratory tree, from the nasal cavity to the bronchi, is lined by pseudostratified columnar ciliated epithelium, while the alveolar region is lined by a thin layer of squamous epithelial cells that enable gas exchange. Mechanisms such as cilia motility, muscle contraction, mucus secretion, and antibacterial functions serve to maintain continuous physical clearance at airways. The respiratory barrier also benefits from mucociliary escalators, intercellular protein junctions, and secreted antimicrobial products.^{11,28} The intestinal barrier, on the other hand, exhibits selective permeability, specialization for absorption and exchange, and local defense against microbes and toxins.^{11,32}

While the structure and function of epithelial tissues vary between the skin, respiratory tract, and gastrointestinal system,³³ the mechanisms safeguarding epithelial integrity share remarkable similarities between species.^{34–36} For instance, porcine skin closely resembles human skin in terms of structure, thickness, hair follicle density, pigmentation, and collagen and lipid composition.^{35,36} Human and pig skins display similar mean epidermal thickness (~52 μ m and ~75 μ m, respectively) with comparable *stratum corneum* thickness,³⁶ histological characteristics, and hair follicle density.³⁴ Structurally, pig skin bears the closest resemblance to human skin, as evidenced by similar keratinocyte proliferation rates of 1.73% in pig skin compared to 1.45% in human skin. However, notable structural and functional differences exist among various species (Table 1). Most assessments have focused on comparing rodent and non-rodent species, highlighting crucial functional differences such as the predominant eccrine sweat glands in humans versus apocrine glands in pigs, underscoring the significance of using these animals in experiments that mimic human biology.³⁷ These apocrine glands in pigs extend into the subcutis and play a minimal role in thermoregulation.³⁸ Rabbit skin is uniquely thin, with an epidermis and *stratum corneum* about one-third and one-fifth the thickness of human skin, respectively, and features a thinner basal and more extensive granular layer compared to humans and pigs.³⁶ The thickness of the oral mucosa's epithelium and the depth of rete ridges generally correlate with species size, with rodents displaying variable epithelial thickness and typically flat rete ridges. Non-rodents have denser epithelial layers and more pronounced rete ridges, with layer counts ranging from 8 to 40 across species such as dogs, rabbits, minipigs, monkeys, and humans. While rodents often exhibit keratinized epithelium, non-rodent species typically have a nonkeratinized mucosal lining, similar to humans, though rabbits have a small keratinized area in the cheek epithelium.³⁹ Rabbit skin features higher keratinocyte proliferation rates than both human and pig skin, while rodent skin differs significantly from human skin due to its loose connection to the subcutaneous connective tissue.^{35,36,40}

In dogs and cats, the majority of the skin surface is obscured by fur, resulting in a comparably thin epidermis.^{41,42} These animals typically have compound follicles grouped in clusters of one to six, commonly featuring three primary follicles along with several smaller secondary follicles. Breed variations exist; for instance, German Shepherds generally have more secondary follicles compared to short-coated breeds like Terriers. Cats usually have between 10 and 20 secondary follicles, which is more than dogs, with between 2 and 15 follicles.⁴¹ Haired skin has a thinner epidermis, whereas non-haired skin of the nose and paw pads has a thicker epidermis.^{42,43} Notably, skin thickness varies significantly across different body areas in both dogs and cats, reflecting a range of physiological factors. For dogs, the average skin thickness ranges from 0.5 mm to 5.0 mm, whereas for cats, it ranges from 0.4 mm to 2 mm.^{42,44} This variation is influenced by several factors, including the breed, specific anatomical locations on the body, the sex and age of the animal, and the level of skin hydration.^{42,45} The *stratum corneum* is approximately 3–35 μ m in cats and 5–150 μ m in dogs.⁴² Cats possess more sebaceous glands on their faces and have smoother digital pads due to a compact layer of *stratum corneum*, whereas dog's digital pads feature conical papillae that align with the epidermal surface. Additionally, both species have apocrine sweat glands associated with hair follicles across their bodies, which may be involved in pheromone release.^{41,42}

In general, the preservation of the epithelial barrier's integrity against harmful environmental agents is achieved through the presence of tight junctions (TJs), adherens junctions (AJs), and desmosomes, which among their various functions, play a role in sealing intercellular gaps. This “gate and fence” function is characterized by an intricate arrangement of polymorphic transmembrane proteins (such as occludins, tricellulins, claudins, and junctional adhesion molecules), which engage with the cytoskeleton through adaptor proteins [zonula occludens (ZO)-1, ZO-2, and ZO-3].^{11,33,46,47} Damage to these junctions disrupts epithelial balance and thus the permeability of the epithelial barrier increases along with inflammation, involving both type 1 and type 2 immune responses. Type 1 response leads to leakage at TJs due to cytokines such as TNF. Type 2 response

TABLE 1 Comparison of the general skin structure, thickness, types of sweat glands, and the presence of specific skin layers across humans, pigs, rabbits, mice, and dogs.

Feature	Human	Pig	Rabbit	Mouse	Dog
Epidermal thickness	Moderate	Moderate	Thinner	Thinnest	Moderate
Dermis thickness	Thick	Thick	Moderate	Thin	Thick
Hair follicle density	Low	Moderate	High	High	High
Sweat glands	Eccrine	Both eccrine and apocrine ^a	Apocrine	None	Apocrine
<i>Stratum corneum</i> thickness	Moderate	Moderate	Thin	Very Thin	Thick
Subcutaneous fat	Present	Present	Present	Less Present	Present
Collagen organization	Organized	Organized	Less Organized	Disorganized	Organized
Sebaceous glands	Present	Present	Present	Present	Present
Proliferation index	Moderate	Moderate	Higher	Higher	Moderate

Note: Reference: ^{35–37, 39, 316}

^aPigs possess both types of sweat glands, however they predominantly have apocrine glands.

enhances permeability via the pore pathway, mediated by cytokines such as IL-4 and IL-13 generated by activated ILC2s triggered by alarmins (IL-25, IL-33, and TSLP)^{11,14,46,48,49} (Figure 1).

Epithelial cells produce cytokines that activate other effector cells such as sentinel cells and endothelial cells initiating the inflammatory cascade.^{50–52} They may also secrete cytokines that increase the activity of effector cells such as neutrophils and macrophages. The types of cytokines may differ according to the initiating insult, such as the type of pathogen, and may drive different inflammatory responses. Helminthic infections are widely seen in companion animals and humans, especially in developing countries.⁵³ Infection with helminths results in a type 2 inflammatory response with a unique cytokine signature composed mainly of IL-4, IL-5, and IL-13 leading to goblet cell hyperplasia, increased mucin production, increased smooth muscle contractility, and increased epithelial cell turnover which leads to an expulsion response against the worms.⁵⁴ Although this unique cytokine signature is released by ILC2 and type 2T-helper cells, the signals that drive the immune system towards a type 2 reaction are derived from the encounter of the damaged epithelia with parasitic subunits and antigens.^{2,55,56}

Fungal pathogens are known to aggravate allergic diseases alongside their potential for infection and intoxication. *Aspergillus* spp. antigens may cause sensitization in atopic patients with asthma leading to allergic bronchopulmonary aspergillosis (ABPA),⁵⁷ and increased severity of asthma attacks.⁵⁸ IL-33 is released from bronchial epithelial cells in response to *Aspergillus* spp. antigens, which act as proteases resulting in the initiation of type 2 immunity and ABPA.⁵⁹ Recurrent airway obstruction in horses has been associated with moldy hay and sensitization to *Aspergillus* spp.^{60,61} *Alternaria* spp. antigens are significant allergens that can cause sensitization in atopic individuals, leading to severe asthma and respiratory conditions. This sensitization is linked to increased asthma severity and the risk of life-threatening exacerbations in response to exposure to *Alternaria* spores, particularly during thunderstorms.⁶² In response to *Alternaria* antigens, which act as proteases, airway epithelial cells release proinflammatory cytokines such as IL-1B, IL-6, IL-8,^{63,64} and type 2-triggering cytokines (alarmins) such as IL-33, TSLP, and IL-25.⁶⁵ This cytokine release leads to barrier damage and exacerbation of the disease.

Many enteric pathogenic bacteria cause epithelial damage as the first step in the disease pathogenesis, be it through a secreted toxin, or direct invasion of the epithelium. Enterohemorrhagic *E. coli*, secretes a shiga-like toxin causing the inhibition of 60S subunit assembly in eukaryotic ribosomes, through binding of 28S rRNA, leading to translation cessation and cellular damage.⁶⁶ Common intestinal pathogens for both humans and dogs such as *Salmonella* spp. and *Campylobacter* spp.,⁶⁷ cause intestinal barrier disruption by direct invasion of epithelial cells and cellular damage, leading to gastroenteritis, albeit dogs have no to mild symptoms in comparison with humans. The healthy microbiome, consisting of bacteria and fungi in humans and companion animals, is critical for maintaining homeostasis in the body. The disturbance of the epithelial layer disrupts the delicate balance of the healthy microbiome, reducing its diversity

and paving the way for colonization by pathogenic microorganisms, most notably *Staphylococcus aureus*.^{68,69} This microbial imbalance, called dysbiosis, can intensify the inflammatory response, creating a vicious cycle⁷⁰ (Figure 2).

The focus on epithelial damage and signalling induced by viral infections has greatly increased following the COVID-19 pandemic. This pandemic has posed a significant threat to global health, affecting both humans and animals and highlighting the complex interplay between viral infections and immune responses. In humans, the aberrant release of cytokines leading to a hyperinflammatory cytokine storm is the main cause of fatalities from SARS-CoV2 infections.⁷¹ The main cytokines associated with severe COVID-19 are IL-6, IL-8 and TNF- α .^{72,73} Although IL-1B was increased in the sera of patients with COVID-19, it was not independently significant for predicting overall survival.⁷³ It was shown that the elevated IL-1B was due to two-hit inflammasome activation in myeloid-derived cells, the second hit coming from dsDNA released by airway epithelial cells. IL-1B in turn resulted in the release of IL-6 from epithelial cells leading to the aforementioned cytokine storm in humans.⁷⁴ From the perspective of companion animals, it has been documented that both dogs and cats can host COVID-19. Dogs may shed small amounts of SARS-CoV-2 from nasal and oral swabs without displaying symptoms, whereas cats demonstrate a higher susceptibility to the virus in clinical scenarios compared to dogs.⁷⁵ In instances of canine infection, transmission is likely to be minimal. Additionally, dogs with owners who tested positive for SARS-CoV-2 may have had a higher likelihood of exposure during outbreaks.⁷⁶ Understanding the mechanisms of epithelial damage and cytokine signaling in viral infections is crucial for developing effective strategies to mitigate the health impacts of diseases.

3 | THE EPITHELIAL BARRIER THEORY IN THE CONTEXT OF COMPANION ANIMALS

The epithelial barrier theory proposes that hazardous substances introduced into humans through a combination of dietary and lifestyle habits stress the epithelial lining and thereby contributes to an increased barrier permeability, microbial dysbiosis, translocation of bacteria to inter- and subepithelial areas, tissue microinflammation, and a proinflammatory immune response⁷⁷ (Figure 2). The recent rise in chronic non-communicable diseases including autoimmune and allergic disorders is linked to epithelial barrier damage from harmful environmental agents, exacerbated by changes in the human exposure due to industrialization and modernization. (Box 2). Numerous studies illustrate how these environmental factors compromise the integrity of the epithelial barrier, ultimately resulting in an increase in the number of patients and growing burden on healthcare systems.^{3,10–12,14,78–87} The recent concepts of epithelial barrier theory encompass several key mechanisms. Molecular toxicity occurs at significantly lower doses of substances, leading to adverse effects. Epithelitis involves inflammation of the exposed surface layer, accompanied by the release of alarmins and chemokines.

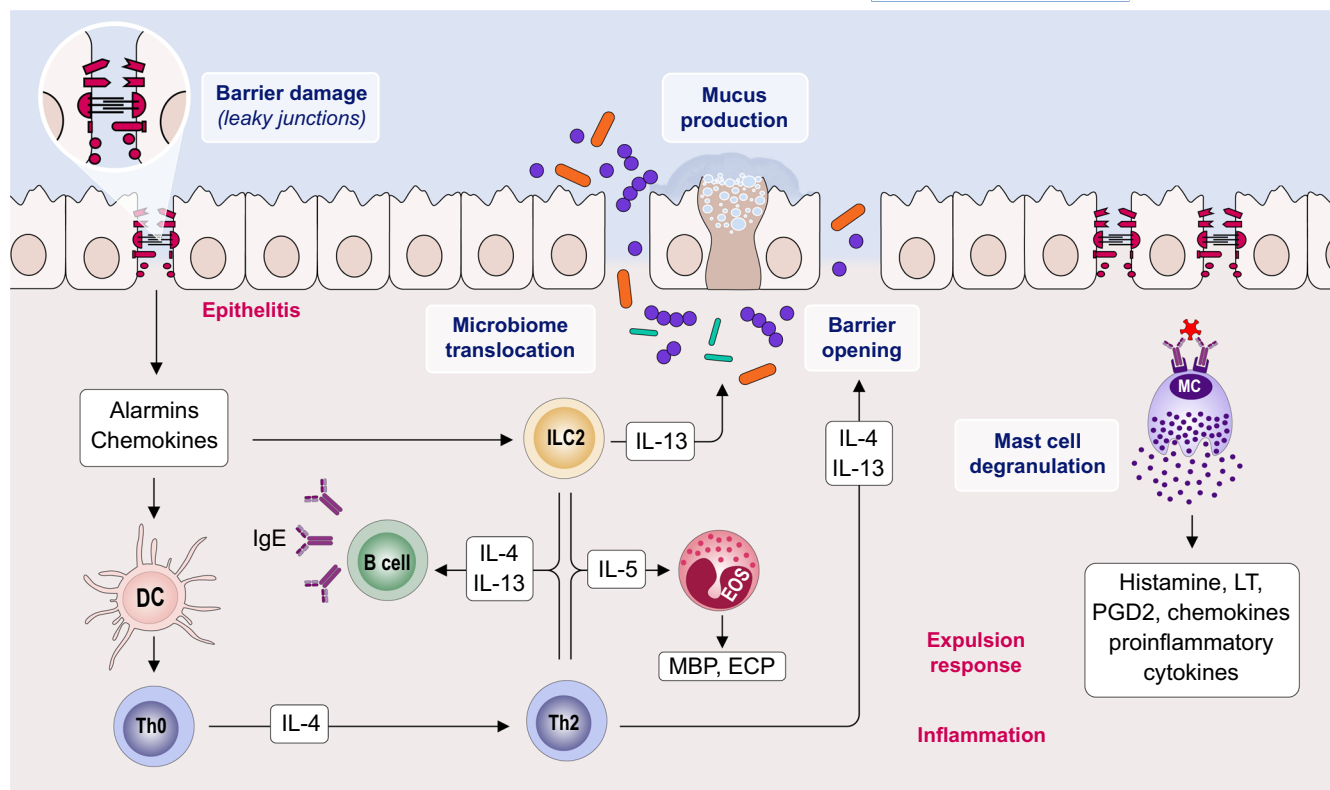


FIGURE 1 Immune mechanisms underlying epithelial barrier disruption: Exosome-induced integrity loss, epithelitis development, and alarmin release. The epithelial barrier may be compromised by a range of allergens, pathogens, and environmental pollutants. These include toxins present in laundry, dishwashing, and household cleaning products, as well as allergens from house dust mites, and certain bacteria, fungi, and viruses. Epithelial barrier damaging agents from the environment lead to microbial dysbiosis and the translocation of commensal and opportunistic pathogens across epithelial barriers often trigger a type 2 immune response. This response is marked by the dominance of Th2 cells, type 2 ILC2s, and eosinophils. Mast cells, macrophages, and antibody-producing B cells may also participate in this process. In this setting or under continuous exposure, the epithelium fails to completely repair and seal the barrier, creating leaky barriers, microbial dysbiosis, and chronic inflammation. Damaged epithelial cells release alarmins such as IL-25, IL-33, and TSLP, leading to the activation of ILC2 and Th2 cells. Activated cells promote type 2 skewing and stimulate B cells to produce IgE. Type 2 cytokines and mast cell degranulation intensify the inflammation and further weaken barrier function. EOS, eosinophil, BAS, basophil, MC, Mast cell, MBP, major basic protein, ECP, eosinophilic cationic protein, TSLP, thymic stromal lymphopoietin, DC, dendritic cell, ILC2, innate lymphoid cell-2, LT, leukotrienes, PGD2, Prostaglandin D2, Th0, naive T cell, Th2, T helper 2, Ig E, immunoglobulin E.

Additionally, circulating micro-inflammation is observed in roughly one-third of humans, characterized by elevated levels of cytokines and chemokines in the bloodstream.² Furthermore, the expulsion response, which closely resembles the process of expelling parasite larvae, involves mechanisms to eject translocated microbiome elements and prevent sepsis (Figure 2).

As mentioned before, domestic animals, especially pets, live alongside humans and are exposed to the same environmental factors brought about by modernization and urbanization. Indeed, it can be postulated that in some cases, companion animals may be exposed to more of these chemicals than their human counterparts. First, companion animals, especially those living in households, may come across detergents and surfactants (from surface cleaners) at remarkably higher doses. Although the fur structure of cats and dogs provides them with an extra barrier, the underside of their paws is mostly furless (some breeds, such as Samoyed, Alaskan Malamute, and Siberian Husky, can have higher fur content under the paws). This may cause animals walking barefoot on the ground to

be more exposed to surface cleaners, detergents, and surfactants. This interpretation may be partially substantiated by diseases such as canine AD, which are common in animals at the palmar surface of the paws. Notably, common sites of pruritus include the interdigital areas of the paws, carpi, tarsi, axillae, ventrum, face and groin.⁸⁸ These regions also have high-contact with the surfaces of the home. Secondly, there is a growing use of cosmetics designed specifically for pets, which often undergo less rigorous testing and dose adjustments than products for human use. Thirdly, it is evident that dogs and cats may be more intensively exposed to detergents and surfactants via oral/buccal mucosa, particularly when they lick their paws or swallow pet toothpaste [commonly containing sodium lauryl sulfate (SLS)]. Therefore, pets can come into contact with these chemical ingredients more frequently and in larger quantities. It should be acknowledged that animals are affected by air pollution and micro- and nano-plastics just like humans. Ground-level pollution may be more detrimental due to precipitated air pollution constituents [ozone (O₃) and exhaust gas exposure]. Given that companion

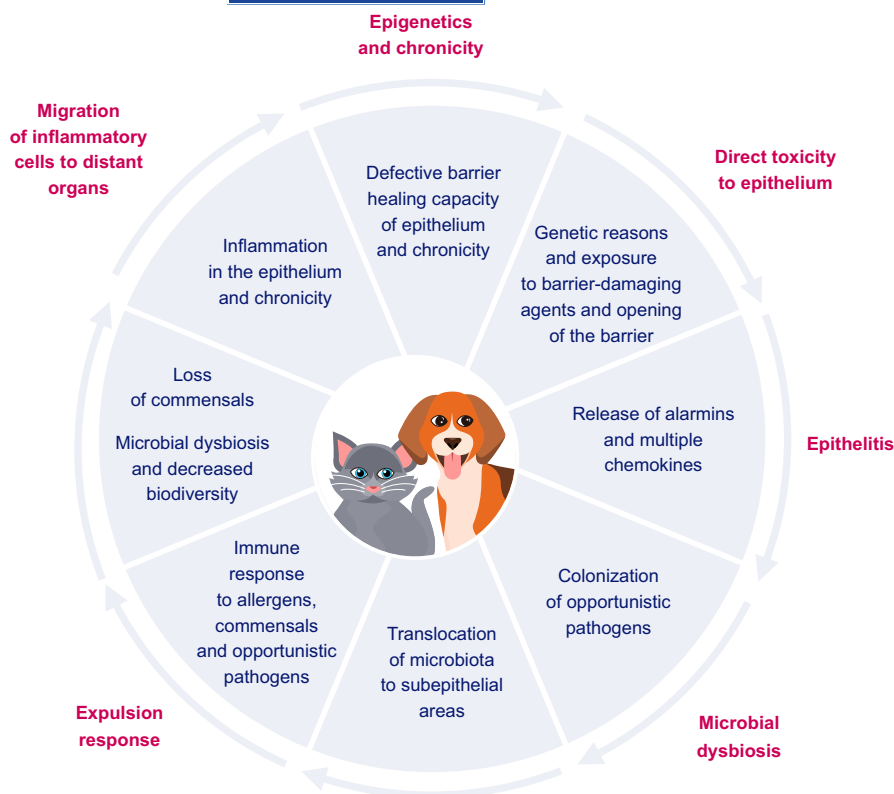


FIGURE 2 A cascade of interconnected events initiates a relentless cycle leading to enduring peri-epithelial inflammation and compromised barrier integrity. According to the epithelial barrier theory, after impairment of the barrier and epithelitis, a sequence of events unfolds. This includes persistent immune responses to allergens and the development of tissue microinflammation, both implicated in the initiation of allergic, autoimmune, and metabolic disorders. The immunopathological mechanisms that elucidate these diseases are expounded by the epithelial barrier theory. This revelation is significant not only for humans but also for companion animals that inhabit the same environment.

BOX 2 Selection criteria of epithelial barrier theory related diseases

- Increased prevalence after 1960s or 2000s not accounted for by improvements in diagnostic methods.³
- Microbial dysbiosis with loss of commensals and colonization of opportunistic pathogens.
- Circulating microinflammation.
- Epithelial barrier defect and epithelitis (IL-1, IL-25, IL-33, TSLP).
- Appearance of these diseases in multimorbidities in the recent years.^{3,13}

animals are closer to the ground, especially breeds such as Miniature Dachshund, Basset Hound, and Chihuahua, they may also sustain greater exposure to many chemicals. Another essential point not to be overlooked is that most equipment for pets, such as bowls and toys, is made from plastics, which can be a source of microplastic exposure. Indoor air pollutants, including volatile organic compounds (VOCs), allergens, tobacco smoke, and microorganisms, may be even more dangerous to companion animals. As some animals, mostly cats, spend their entire lives indoors, they experience continuous exposure to indoor pollution (Table 2). Many households have more than one pet. Maintaining multiple pets in the same household can lead to more frequent use of cleaning agents. Moreover, the cohabitation of cats and dogs may introduce unique exposure pathways. For example, dogs often bring in outdoor contaminants that could

TABLE 2 The potential differences in the exposome between pets confined indoors and those residing primarily outdoors.

Exposure	Pets living mostly outdoors	Pets living indoors only
Food additives	✓✓✓	✓✓✓
Detergents	✓✓	✓✓✓
Household cleaners	–	✓✓✓
Pet cosmetics	✓✓	✓✓✓
Micro- and nano-plastics	✓	✓✓✓
Indoor pollution	–	✓✓✓
Outdoor pollution	✓✓✓	✓✓
House dust mites	–	✓✓✓
Pollens	✓✓✓	✓
Parasites	✓✓✓	✓
Food allergens	✓✓	✓✓✓
Microbiome	✓✓✓	✓

Note: –, negligible, almost non-existent; ✓, rare; ✓✓, occasional; ✓✓✓, common.

affect indoor cats, who are generally less mobile and spend more time grooming, thus potentially ingesting more of certain chemicals. In addition, there have been numerous reports of indoor toxic exposure incidents involving domestic animals. Insecticides, especially anticholinesterase compounds, and anticoagulant rodenticides are often implicated in poisoning cases. Additionally, molluscicides, such as metaldehyde, along with various household products, have exhibited a stable or increasing trend in incidents of poisoning.⁸⁹ Even gardening practices present substantial risks to domestic animals.

Research has indicated that pet dogs are commonly exposed to lawn chemicals (such as herbicides), which have been detected in their urine, suggesting potential contact with the urothelium.⁹⁰ Ultimately, the well-being of humans, animals, and the environment is intertwined, as recognized by the One Health Initiative, which is defined as an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems.^{22,23}

The perspective of the epithelial barrier theory can readily be extended to companion animals under the One Health umbrella. A recent meta-analysis of 22 chemical inventories in 19 countries showed that over 350,000 new substances have become part of human life since the 1960s, and there has been limited oversight regarding their potential toxicity.⁹¹ These chemicals have intense adverse effects not only on humans but also on animals, and the entire ecosystem (Figure 3). A comprehensive epidemiologic study including 22,333 dogs, has confirmed that skin problems and enteropathies are commonly diagnosed disorders.⁹² The role of the aforementioned chemicals on the rising occurrence of these conditions, which can be directly linked to the disturbance of epithelial barriers, should not be underestimated.

Environmental factors including global warming, climate change, air pollution, plastic burden and reduced biodiversity pose significant health threats, particularly in relation to non-communicable diseases such as allergies. Average global temperatures are rising due to increased levels of human-made greenhouse gases in the atmosphere, particularly CO₂. The increase in Earth's temperature is demonstrated by the warming oceans, melting glaciers, rising sea levels, and reduced snow cover in the Northern Hemisphere.^{93,94} Environmental shifts are evident in the frequency, intensity, and type of precipitation, along

with extreme weather events such as heat waves, droughts, floods, blizzards, thunderstorms, sandstorms, and hurricanes.⁹³ These challenges pose threats to human life and significantly impact companion animals sharing the same environment. Climate change contributes to rising sea levels, extreme weather events, and crop yield reduction, impacting food security and causing deficiencies in zinc, iron, and protein. Furthermore, elevated CO₂ levels promote allergenic pollen growth.⁴ While extensively documented in humans, this condition has not undergone thorough investigation in animals. To the best of our knowledge, this is the first paper that comprehensively examines substances damaging the epithelial barrier in companion animals, their possible origins, and the relevant molecular mechanisms, within the context of the current understanding of the epithelial barrier theory. We emphasize the utility and necessity of conducting analogous studies within animal populations.

4 | COMMON EXPOSOME IN HUMANS AND DOMESTIC ANIMALS: ENVIRONMENTAL FACTORS AFFECTING THE EPITHELIAL BARRIERS

4.1 | Gastrointestinal barriers: Enzymes and emulsifiers in processed foods and food additives for pets

Even with the diverse range of immune mechanisms that maintain intestinal homeostasis, chronic inflammation can occur due to impairments in this system. Comparative pathological studies

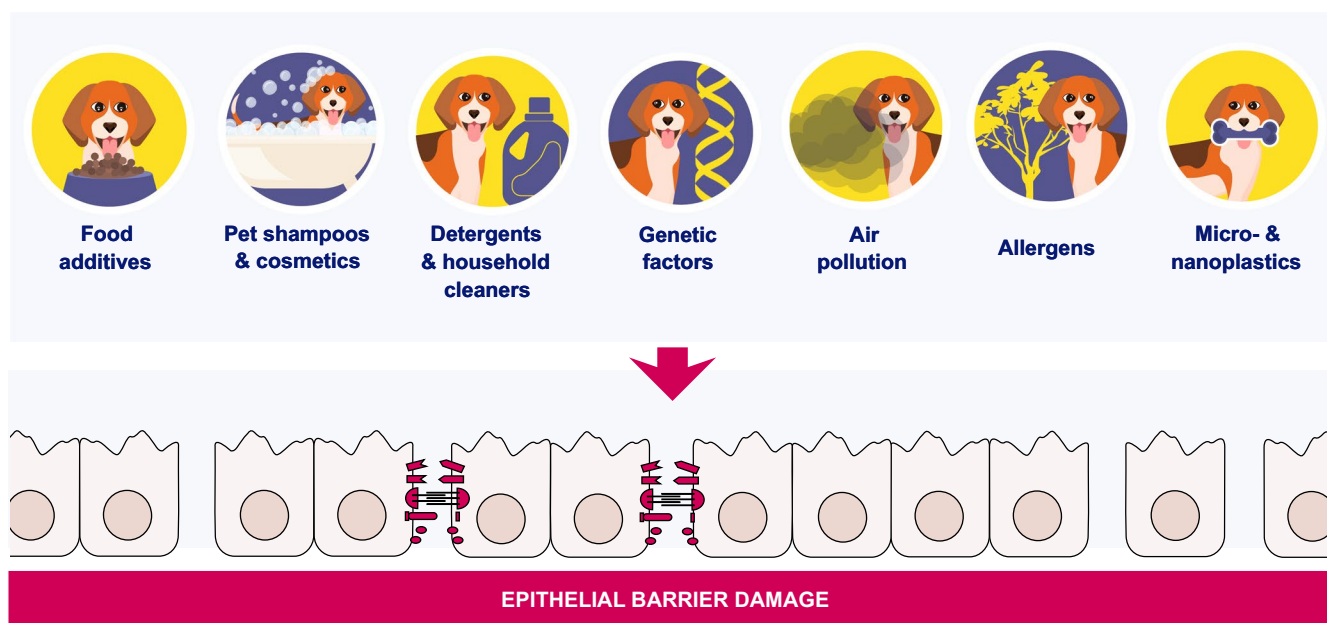


FIGURE 3 Influencing factors on epithelial barrier integrity. The integrity of the epithelial barrier is susceptible to various allergens, pathogens, and environmental pollutants. These encompass toxins present in laundry, dishwashing, and household cleaning products, as well as allergens from house dust mites, specific bacteria, fungi, and viruses. Furthermore, surfactants, enzymes, and emulsifiers in processed food, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles, and microplastics can also compromise the epithelial barrier.

can also serve as crucial guides to understanding the functioning of biological systems. For instance, IBD, which encompasses both Crohn's disease and ulcerative colitis, is highly prevalent in humans and is also present and often investigated in animals. Comparable disorders are observed across various animal species with particular significance attached to the occurrence of IBD in dogs due to its high prevalence and similarities to humans. In dogs, the development of IBD originated as a result of dysregulation of mucosal immunity in predisposed animals.⁹⁵ It is commonly accepted that the etiology of IBD is directly related to specific environmental factors that trigger intestinal inflammation in genetically susceptible individuals.^{96,97} Here, it should be noted that the testing and dose adjustments for food additives in pet products and chemical ingredients in cosmetics are generally less stringent compared to those for human use and consumption. Thus, pets can encounter these chemical ingredients more frequently and potentially in greater quantities.

The pathomechanisms underlying gastrointestinal disorders in humans and pets are quite similar. The loss of tolerance to antigens, such as food and intestinal bacteria, is one of the most studied mechanisms that could explain the development of chronic intestinal inflammation.⁹⁵ Although the main dynamics bear similarities between humans and dogs, certain molecular differences are evident. For instance, unlike in humans, there is mixed activation of T helper (h) 1 and Th2 in dogs,^{95,98–100} leading to different expression of some cytokines and it has recently been hypothesized that different Th cells can be involved in different IBD types. The consumption of food additives by humans has significantly risen in recent decades, and a similar trend is likely occurring among companion animals.¹⁰¹ A recent study using human organoids and organo-chips clearly demonstrated direct evidence of the detrimental effects of food emulsifiers polysorbate 20 (P20) and polysorbate 80 (P80) on intestinal epithelial integrity, even in low doses.⁷⁷ Although there was a human focus in this study, the mentioned doses in induced pluripotent stem cell organoids and organo-chips are quite applicable to domestic animals. Polysorbates are extensively used food additives to stabilize functional components and flavorings, subsequently improving shelf life for pet food. They are frequently incorporated into pet foods, especially polysorbate 60 (P60, E435) and P80 (E433), particularly in moist formulations such as those found in cans, sachets, and other packaging types. Their primary function is to prevent the separation of ingredients, ensuring a consistent texture and appearance across the product in canned pet foods.¹⁰¹ Additionally, polysorbates play a crucial role in creating the appealing gravy or gel-like consistency that characterizes many wet pet foods. This not only enhances the visual appeal but also improves the palatability and acceptability of the food to pets (Table 3). P60 and P80 are utilized either on their own or in conjunction with sorbitan monostearate as an emulsifier in mineral premixes and dietary supplements intended for animal feeds. They are also used as an emulsifier in milk-replacer formulations for calves.¹⁰²

Food additives encompass natural, semi-synthetic, or synthetic substances, including biotechnological products, which are present

in edible food items either through deliberate inclusion or as a result of the food's processing or packaging. These additives enhance the technological attributes of food products and extend their shelf life, yet they can inflict significant harm to living tissues. Here, it should be noted that frequently used non-absorbed food additives also interact with the microbiota at higher levels.^{103,104} Detrimental alterations in microbiota can subsequently promote chronic inflammatory diseases, such as metabolic syndrome and IBD.¹⁰⁴ The negative effects of emulsifiers have been substantiated by in vivo studies. P80 triggered mild inflammation and led to obesity and metabolic syndrome in wild-type mice.¹⁰⁵ Furthermore, it exacerbated severe colitis in predisposed mice. P80 has also been shown to increase the susceptibility of the small intestine to injury caused by indomethacin by inducing dysbiosis in the ileum.¹⁰⁶ The offspring of P80-treated mother mice have been shown to be more vulnerable to dextran sulfate sodium-induced colitis, which is indicative that maternal P80 intake could induce gut dysbiosis and promote colitis susceptibility in adulthood.¹⁰⁷

Similar to P80, carboxymethylcellulose (CMC), another emulsifier commonly used to enhance texture and extend shelf life, causes microbiota impairment that leads to intestinal inflammation. When administered to mice, both CMC and P80 led to the intrusion of microbiota into the mucus, changes in microbiota composition, including an increase in bacteria producing proinflammatory flagellin and LPS, and the development of persistent inflammation.^{77,105,108–110} An enrichment of genes related to flagella and bacterial motility has been found in the gut microbiome.^{77,111,112} From a mechanistic aspect, intestinal microbiota is a direct target of P80 and CMC. When microbiota treated in vitro with CMC or P80 are transferred to germ-free recipient animals, they undergo detrimental changes that can ultimately result in chronic intestinal inflammation.^{104,105,108,113} In wild-type mice exposed to relatively low concentrations of CMC, mild inflammation and obesity/metabolic syndrome were induced, while in IL-10^{-/-} and toll-like receptor (TLR) 5^{-/-} mice, an exacerbation of severe colitis was observed. The study revealed that prolonged exposure to CMC led to the deterioration of the mucosa protective function, greater bacterial adherence, and a mouse microbiota with a heightened pro-inflammatory profile.¹⁰⁸

Carrageenan is another extensively used food additive for its gelling, thickening, and stabilizing properties. It has originated from a group of high molecular weight sulfated polysaccharides extracted from seaweeds. Carrageenan is commercially used to improve the texture of food products including infant formulas, dairy products, milk alternatives such as almond milk, processed meats, and soy-based products.¹¹⁴ Carrageenan and CMC are frequently used in commercial food products as an alternative to other forms of dietary fiber like water-insoluble cellulose and resistant starch, or water-soluble fiber such as pectin and raffinose. Previous studies conducted in rodents emphasized the adverse effects of carrageenan.¹¹⁴ Consistent with other food additives, microbiota plays a crucial role in elucidating the effects of carrageenan exposure. For instance, animals previously immunized with *Bacteroides vulgatus* exhibited a faster onset of experimental ulcerative colitis and more

TABLE 3 List of additives commonly used in pet foods and their properties.

Additive	E-number	Source	Purpose of usage
Acacia gum	E414	Naturally derived	Stabilizer, thickener, gelling agent, binder
Aluminium silicate	E559	Naturally derived	Anti-caking agent
Anthocyanins	E163	Naturally derived	Antioxidant preservative Coloring agent
Benzoic acid	E210	Synthetic	Antioxidant preservative pH adjustment
Betanin/Beetroot red	E162	Naturally derived	Coloring agent
Butylated hydroxyanisole (BHA)	E320	Synthetic	Antioxidant preservative
Butylated hydroxytoluene (BHT)	E321	Synthetic	Antioxidant preservative
Calcium disodium ethylene diamine tetra-acetate (EDTA)	E385	Synthetic	Chelating agents
Caramels	E150a-d	Synthetic	Coloring agent
Carboxymethylcellulose (CMC)	E466	Synthetic	Emulsifier
Carmine/Cochineal	E120	Naturally derived	Coloring agent
Carotenoids	E160 a-e	Naturally derived	Antioxidant preservative
Carrageenan	E407	Naturally derived	Emulsifier
Cassia gum	E427	Naturally derived	Stabilizer, thickener, gelling agent, binder
Calcium propionate	E282	Synthetic	Antimicrobial preservative
Cellulose derivatives	E460-469	Synthetic/ Naturally derived	Stabilizer, thickener, gelling agent, binder Anti-caking agent
Citric acid	E330	Naturally derived	Antioxidant preservative
Curcumin	E100	Naturally derived	Coloring agent
Disodium 5 ribonucleotides	E635	Synthetic	Flavor enhancer
Ethoxyquin	E324	Synthetic	Antioxidant preservative
Gelatin	E441	Naturally derived	Stabilizer, thickener, gelling agent, binder
Glutamic acid	E620	Naturally derived	Flavor enhancer
Glycerin	E422	Naturally derived	Humectant
Guanosine monophosphate	E626	Synthetic	Flavor enhancer
Guar gum	E412	Naturally derived	Stabilizer, thickener, gelling agent, binder
Iron oxides and hydroxides	E172	Naturally derived	Coloring agent
Modified starch	E1401-1404	Synthetic	Emulsifier
Monosodium glutamate	E621	Synthetic/ Naturally derived	Flavor enhancer
Patent blue V	E131	Synthetic	Coloring agent
Pectin	E440	Naturally derived	Stabilizer, thickener, gelling agent, binder
Pentasodium triphosphate	E451	Synthetic	Stabilizer, thickener, gelling agent, binder
Polyglycerol polyricinoleate (PGPR)	E476	Synthetic	Emulsifier
Polysorbate 60 (P60)	E435	Synthetic	Emulsifier
Polysorbate 80 (P80)	E433	Synthetic	Emulsifier
Potassium alginate	E402	Synthetic	Stabilizer, thickener, gelling agent, binder
Potassium sorbate	E202	Synthetic	Antimicrobial preservative

(Continues)

TABLE 3 (Continued)

Additive	E-number	Source	Purpose of usage
Ponceau 4R	E124	Synthetic	Coloring agent
Propyl gallate	E310	Synthetic	Antioxidant preservative
Pyrophosphates	E339	Synthetic	Flavor enhancer
Rosemary extract	E392	Naturally derived	Antioxidant preservative
Silicon dioxide	E551	Naturally derived	Anti-caking agent
Sodium alginate	E401	Synthetic	Stabilizer, thickener, gelling agent, binder
Sodium aluminosilicate	E554	Synthetic	Anti-caking agent
Sodium nitrite	E250	Synthetic	Flavor enhancer Antimicrobial preservative
Sodium sorbate	E201	Synthetic	Antimicrobial preservative
Sorbitol	E420	Naturally derived	Artificial sweetener
Sorbitan monostearate	E491	Synthetic	Emulsifier
Soya lecithin	E322	Naturally derived	Emulsifier
Sulfites	E220-228	Synthetic	Antioxidant preservative
Sunset yellow	E110	Synthetic	Coloring agent
Tartrazine	E101	Synthetic	Coloring agent
Titanium dioxide	E171	Naturally derived	Coloring agent
Vitamin C (ascorbic acid)	E300-E305	Naturally derived	Antioxidant preservative
Vitamin E (tocopherols)	E306-309	Naturally derived	Antioxidant preservative
Xanthan gum	E415	Naturally derived	Stabilizer, thickener, gelling agent, binder

Note: Reference: ^{101, 102, 127}

severe lesions when subsequently given carrageenan compared to animals that received carrageenan alone.¹¹⁵ The participation of TLR4 and IL-6 in the innate immune response to carrageenan was studied through experiments involving TLR4- and myeloid differentiation primary response 88-deficient mice. κ -carrageenan enhances LPS-induced IL-8 secretion via the Bcl10-NF- κ B pathway, as demonstrated by its exacerbation of *Citrobacter freundii* DBS100-induced colitis in mice.¹¹⁶ Notably, carrageenan serves as a common gelling agent in canned dog and cat food.¹⁰¹ As mentioned above, animal studies indicated that food emulsifiers like carrageenan could serve as a potential conditional inflammatory factor, amplifying any pre-existing chronic inflammation of the intestinal tract induced by pathogens.

In addition to emulsifiers, a wide variety of additives, whether of natural or synthetic origin, are employed in the food for companion animals. Numerous chemicals are not only prevalent in packaged dry or canned pet food but are also present in treat or reward foods. They are commonly utilized as antioxidants, sweeteners, gelling agents, adsorbent clays, antimicrobial preservatives, coloring and flavoring compounds (Table 3). Even though certain substances are prohibited for human consumption, they are still employed in the production of cat and dog foods.¹⁰¹ For instance, ethoxyquin had been used as an antioxidant in animal feeding for years. A metabolite of ethoxyquin has been identified as potentially genotoxic, and an impurity linked to ethoxyquin has been designated as a potential

mutagen by the European Food Safety Authority.^{101,117} In 1997, the FDA's Center for Veterinary Medicine requested that the American pet food industry reduce the maximum allowable level of ethoxyquin in dog food.^{118,119} Ultimately, the European Union has banned the use of ethoxyquin as a feed additive for all animal species and categories since June 2020.¹²⁰

Pet foods are typically accessible in three forms, which are moist, semi-moist, or dry, determined by their moisture content at the end of production. Among them, dry foods are most commonly used and makes up a significant portion of the pet food market. The extended shelf life of dry pet foods results from their low water activity (a_w), which is typically less than 0.60 a_w , ensuring microbial stability. However, dry pet foods are often less appealing to pets compared to moist or semi-moist pet foods, likely due to their reduced flavor. Incorporating specific chemical compounds that enhance flavor characteristics is a very common way for augmenting the palatability of pet foods.¹²¹ Xylitol (E967) is employed in numerous human foods as an artificial sweetener, antibacterial agent, and flavor enhancer. It is also added to medical and dental care products. However, in dogs this sweetener is a powerful trigger of insulin secretion, potentially causing a severe, life-threatening drop in blood glucose levels and liver failure.¹⁰¹ Cassia gum (E427), a gelling agent used widely in pet food, has been restricted to specified levels in animal feed in the EU,^{120,122} because of its potential carcinogenic effect. Potassium sorbate (E202) is a mold inhibitor used

in pet foods. It is deemed safe for dogs and cats when present in semi-moist complete feed at a maximum concentration of 3400mg/kg.¹²³ Both cassia gum and potassium sorbate are considerable irritants for the skin, eyes, and respiratory system.¹²⁴ Synthetic esters derived from p-hydroxybenzoic acid (paraben) are extensively employed as antimicrobial preservatives in human food products. Although it is established that paraben metabolites may contribute to endocrine disruption,¹²⁵ its widespread use in cat and dog foods continues. Titanium dioxide (E171), a synthetic whitening agent, has been demonstrated to penetrate the intestinal barrier in rats, where it participates in the initiation and advancement of the early phases of colorectal carcinogenesis.¹²⁶ As of January 2020, France has prohibited the use of titanium dioxide as a food additive owing to safety concerns. Nevertheless, it is still found in many pet foods and treats. Monosodium glutamate (E 621) is frequently used in human food and has been approved as an additive in animal feed in the EU.^{127,128} There are numerous studies showing the inflammatory and tissue damaging effects of monosodium glutamate.^{129–132} This flavor enhancer has been linked with obesity, metabolic disorders, Chinese Restaurant Syndrome, neurotoxic effects and detrimental effects on the reproductive organs in humans and rodent studies.^{133–136} The list of additives in pet food can readily be expanded, such as cinnamic aldehyde, caramelized sugars, tartrazine, sodium sorbate, propyl gallate, etc. Importantly, while certain substances are prohibited or subject to restrictions in human consumption, their widespread usage in animal foods persists, with insufficient scientific data available for some of these substances.

Although there are considerable differences in the gastrointestinal systems among species (Table 4), the pathogenesis of gastrointestinal tract-related diseases exhibits similarities between humans and companion animals (especially dogs). It is quite possible that similar negative effects of these food additives also affect animals. Indeed, current publications highlight the advantages of conventional nutrition and the adverse consequences of a diet primarily comprised of processed foods in companion animals.^{137,138} In this context, consumption of a high-fat, low-carbohydrate diet based on non-processed meats during early life, coupled with maintaining a normal body condition during puppyhood, showed a significant association with a lower incidence of IBD in adult dogs.¹³⁷ Furthermore, a recent study has shown that feeding a non-processed meat-based diet and giving the dog human meal leftovers and table scraps during puppyhood (2–6 months) and adolescence (6–18 months) are protective against chronic enteropathy later in life.¹³⁸ Notably, the consumption of an ultra-processed dry dog food (kibble)-based diet was significantly linked to a higher incidence of chronic enteropathy in adulthood.¹³⁸ Dry dog food undergoes an ultra-processing procedure that involves heat treatment, rendering, milling, and/or extrusion. It also incorporates various food additives, including emulsifiers, coloring agents, and flavor enhancers.^{101,139–142} The application of heat to foods containing both carbohydrates and proteins results in the generation of Maillard reaction products, including advanced glycation end products (AGEs). These AGEs have immunomodulatory properties and could potentially contribute to the

higher occurrence of diet-related chronic inflammatory conditions in the gastrointestinal tract.^{143,144} Pet owners may select their pets' food based on criteria similar to those they use for their own meals. A very recent study reported that owners show greater concern for their dogs' diets than their own, believing that the consumption of preservatives could be harmful to their pets' health. Surprisingly, owners tend to place more trust in pet food manufacturers than in those producing human food.¹⁴⁵ However, it is evident that the list of additives in pet foods is extensive (Table 3), whilst there are inadequate regulations and dosage guidelines in place. According to the epithelial barrier theory, a Western diet, characterized by its high consumption of ultra-processed foods (consisting of emulsifiers and sweeteners) and refined carbohydrates, has been proposed as a potential factor contributing to the rising prevalence of IBD among humans in industrialized societies.^{3,9} As mentioned earlier, the role of epithelial barrier disruption in non-communicable chronic diseases is also applicable to companion animals that share the same environment with humans. The adverse consequences of additives in commercially processed foods for humans are quite similar to the scenario observed in companion animals consuming processed food.

4.2 | Laundry and dishwasher detergents and household cleaners

Cleaning products are extensively used in daily life, and exposure to its toxic chemicals is detrimental to both humans and domestic animals. Indeed, all living organisms are continuously exposed to these products, but companion animals particularly face extensive exposure to these substances because they share the same environment and often the same household with humans. In the early years of the 20th century, the limited availability of oils for soap production and the quest for more potent cleaning agents prompted the commencement of efforts to develop the first synthetic detergent.^{3,11} The utilization of surfactants and enzymes in laundry, dishwashing, household cleaning products, and industrial applications has surged significantly. Various chemicals have been incorporated over time to enhance the cleaning efficacy of detergents. Addition of surfactants [SLS/sodium dodecyl sulfate (SDS) and sodium dodecyl benzene sulfonate (SDBS)] and enzymes (proteases, lipases, amylases, cellulase) since the 1960s significantly improved the performance of detergents.^{11,146} Currently SLS/SDS and SDBS are used at quite high concentrations although molecular toxicity has been shown in 50,000 times dilutions (Box 3). Many components of detergents are hazardous chemicals due to their potential toxicity to the respiratory system and skin, not only for humans but also for domestic animals. In the modern world, numerous garments and toys have been specifically designed for pets. These items have direct contact with animals, including their skin and oral surfaces. All domestic animals, especially pets, along with their clothing, toys, and particularly their food and water bowls, are regularly exposed to these detergents. Cats are at a higher risk of respiratory issues and skin problems than dogs, likely due to their grooming habits where they lick off

TABLE 4 Comparative analysis of gastrointestinal tract features between animals and humans.

Feature	Human	Rodents	Dog	Pig
Dietary adaptation	Omnivorous	Varies by species; in general, omnivorous, guinea pigs are herbivorous	Carnivorous	Omnivorous
Mouth and saliva	Enzymes in saliva start starch digestion (amylase)	Limited enzymatic activity in saliva; less amylase than humans	No enzymatic activity in saliva	Similar to humans, with enzymatic activity (amylase)
Teeth	Heterodont dentition (incisors, canines, premolars, molars)	Varies by species; rodents have continuously growing incisors	Carnassial teeth for shearing meat; fewer molars	Similar to humans; omnivorous dentition
Esophagus	Muscular tube, peristalsis moves food to stomach	Similar structure, but shorter in length	Shorter and wider than humans	Similar to humans
Stomach	Single chamber, slightly acidic (pH 4–5)	Single chamber, varying pH; rodents have a glandular and non-glandular region	Single chamber, highly acidic (pH 1–2)	Single chamber, similar to humans
Small intestine	Long (6–9 m), 10–11 times body length; divided into duodenum, jejunum, ileum	Varies by species; generally shorter than humans; similar divisions	Similar structure to humans; shorter relative length	Similar structure to humans
Large intestine	Long, pouched, divided into cecum, colon, rectum	Varies by species; guinea pigs and rabbits have large cecum for fermentation	Short relative to body size; less fermentation	Similar structure to humans
Liver and gallbladder	Large liver, produces bile; gallbladder stores bile	Similar structure; rodents have a large liver, no gallbladder in rats	Large liver, produces bile; gallbladder stores bile	Similar to humans
Transit time	24–72 h	12–24 h	8–6 h	24–48 h
Peyer's patches	Present	Present	Present	Present
Enzymatic activity	High enzymatic activity	Varies by species	High protease and lipase activity; low amylase	High enzymatic activity
Absorption efficiency	High	High	High	High

Note: Reference:^{317–322}

BOX 3 The prevalence and toxicity of sodium lauryl sulfate (SLS/SDS) in consumer products of pets and households

- Sodium Lauryl Sulfate (SDS, SLS) is a common component in various household and personal care products.
- First included in powder detergents at a concentration of 10% in 1960, its usage has since expanded to include shampoos and household cleaners at concentrations ranging from 5% to 10%.
- After-2000, some toothpaste formulations began incorporating SLS at around 3%, while it is used in cosmetics and skin cleansers at lower concentrations of 0.5% to 2%.⁸⁶ It may play a role in the increased prevalence of Eosinophilic Esophagitis.
- SLS can also be extracted from common household items such as house dust, pillows, and bed sheets.¹⁴⁸
- Despite its widespread use, SLS has been identified as toxic to cells, organoids, and organ chips, even at a significant dilution of 1:50'000, highlighting a toxic threshold of just 0.002%.^{83,154,155,313}

detergents from their fur, causing further skin and mucosal damage. Anionic and non-ionic detergents irritate the skin, leading to erythema, inflammation, and dermatitis in companion animals.¹⁴⁷ In addition, cats that live permanently in indoor environments may face increased chronic exposure to household chemicals.

Apparently, professional rinse aids are one of the most toxic of these substances. Recently, it has been demonstrated that professional dishwasher rinse aid causes epithelial barrier disruption in gastrointestinal epithelial cells at dilutions up to 1: 20,000.⁸² The toxic compound, alcohol ethoxylate remained in active doses in the dishes and could be extracted. A significant effect on epithelial barrier molecules and proinflammatory cytokines and chemokines and type 2 immune response activation was demonstrated. The major pathways of gene activation in toxic doses were regulation of cell death processes, cell migration, proliferation, adhesion, and immune and inflammatory responses.⁸² One of the major surfactants, SLS/SDS increased ROS production and IL-33 release, which is associated with necrotic cell death.^{86,148} Isothiazolinone derivatives, including methylisothiazolinone, methylchloroisothiazolinone, and benzisothiazolinone, are common biocidal preservatives in household cleaners and toiletries. While their hazard risk is typically mitigated by low concentrations in these products, they can still pose irritant and type IV allergenic risks to people and pets.¹⁴⁷ Moreover, household cleaning products and medical disinfectants have ranked among the most prevalent irritants linked to asthma and respiratory diseases. Pets may come into contact with detergents and other household cleaners by licking surfaces that have been treated, licking their fur or paws after a spill, chewing on containers, or biting into laundry detergent pods.¹⁴⁹ Additionally, inadequately rinsed food and water

bowls that still contain detergent residues can also be significant exposure routes for pets. This might be true not only for cats and dogs but for all domestic species. Here, it should be emphasized that self-licking and grooming behavior in cats and dogs can result in significantly high oral exposure to household cleaners. In this case, these animals may routinely encounter cleaning agents and chemicals at levels much higher than humans, influenced by how often their owners clean their houses or surfaces. Taken together, cumulative scientific evidence suggests that skin contact, inhalation, and ingestion of detergents compromise the barrier functions of the airway and skin epithelium by disrupting their integrity, posing a great danger to companion animals and can be an important underlying cause of many diseases.

4.3 | Pet shampoos and cosmetics

The increased utilization of detergents has significantly elevated the daily exposure of human and companion animals to tissue barrier damaging substances, such as surface-active compounds (e.g., lauryl ether sulfate and SLS/SDS, cocamidopropyl betaine) and preservative agents (isothiazolinone derivatives, quaternium 15 and formaldehyde).¹⁵⁰ As these are extensively used in shampoos, personal care products, and cosmetics, cell toxic surfactants have emerged as one of the primary substances for skin and respiratory exposure. Although equipped with a resilient, multilayered keratinized epithelial layer, the skin remains susceptible to the hazardous effects of detergents. Surfactants, as the main component in detergents, induce the destabilization of the cell membrane by incorporating detergent molecules into the lipid bilayer resulting in bilayer bending and the formation of endo- or exovesiculation. Surfactant molecules completely dissolve the cell membrane by creating micelles in conjunction with membrane phospholipids, leading to the complete disruption of the membrane at elevated concentrations.^{151,152} Ionic surfactants, such as SLS/SDS, cause the denaturation of membrane proteins.¹⁵³ The SLS toxicity raises concerns about its safety and potential effects on human health and the environment.^{154,155} Similar interpretations can be made for surfactants, such as ammonium lauryl sulfate, sodium coco sulfate, and cocamidopropyl betaine which are commonly used for commercial dog and cat shampoos. Although its cellular toxicity has been shown at dilutions as low as 1:50,000, SLS/SDS is being used in relatively high concentrations in pet shampoos such as ~10% (ranging from 1% to 15%). There are also many chemical-containing dry shampoo powders and conditioners on the market, some of which also contain extra odor-preventing chemicals and perfumes.

Healthy skin at an optimal pH provides protection from diseases in all mammals. Several mechanisms contribute to pH regulation of the skin, including fatty acid composition, filaggrin degradation, sodium-hydrogen exchanger (NHE1) activation, and melanosome.¹⁵⁶ The pH level impacts skin barrier function, the synthesis and aggregation of lipids, epidermal differentiation, and desquamation. In humans, the physiological pH of the *stratum corneum* is 4.1–5.8 with

slight differences among face, trunk, and extremities.¹⁵⁷ In general, other mammals exhibit higher pH levels compared to humans (4.1–5.8), such as guinea pigs (pH = 5.5), rats (pH = 6.5), rabbits (pH = 6.7), horses (pH = 7.0–8.0), and monkeys (pH = 6.4). The typical skin pH in dogs ranges from pH 6 to pH 7, but it increases to approximately pH 8–9 in the affected skin of atopic dogs.^{158,159} Healthy cat skin has a pH range between 6.4 and 6.9, with higher values in males than females.¹⁶⁰ Here, it should be noted that the fur of animals forms a highly crucial and robust barrier, but having healthy skin is essential for maintaining a healthy coat of fur. Prolonged and frequent use of primary surfactants commonly found in shampoos alters the skin's natural slightly acidic pH to alkaline values, creating conditions beneficial for the proliferation of pathogenic microorganisms. The majority of pathogenic bacteria linked to skin infections require a pH level exceeding 6 for optimal growth, with growth being inhibited at lower pH values.¹⁵⁶ The restoration of a functional barrier plays a pivotal role in the healing process, and this is where acidification may contribute to improved healing.^{156,161,162} Recently, AD became one of the most common medical conditions in dogs.^{163,164} The complex pathogenesis of AD in dogs can be linked to the epithelial barrier theory. Skin barrier dysfunction and immunological alterations are central to the pathogenesis of canine AD. Several critical aspects warrant consideration when assessing the integrity and robustness of this barrier. Transepidermal water loss (TEWL) is defined as the amount of water that moves from the inner to the outer layers of the skin through the uppermost layers of the epidermis. It serves as a key indicator of compromised barrier function and a crucial factor in allergic sensitization. TEWL is notably elevated in canine AD, highlighting impaired barrier integrity similar to that observed in human AD. Notably, TEWL decreases in atopic dogs whose condition is in remission following treatment, underscoring its importance in understanding the dynamics of skin barrier dysfunction across species.¹⁶⁵ Recently, due to the increased sensitivity and reliability of newer instruments, the preferred noninvasive approach for assessing skin barrier integrity in dogs has shifted from evaluating TEWL alone to concurrently assessing cutaneous pH, hydration, erythema, and TEWL.¹⁶⁶ In addition, a new method, namely the electric impedance spectroscopy is being extensively in humans, and can serve as a useful and robust method for analyzing skin barrier integrity of domestic animals.^{167–169} Furthermore, reduced ceramide levels, major constituents of intercellular lipids in the stratum corneum, are thought to diminish water capacitance of the skin, as observed in dry atopic skin.¹⁷⁰ As part of the lipid component of the skin barrier, ceramides' quantity, spatial arrangement, and diversity are crucial for maintaining the integrity of the skin barrier.¹⁶⁶ In dogs with AD, lower ceramide content associated with elevated levels of TEWL (barrier leakiness), mirroring the condition observed in human AD.¹⁷⁰

Structural proteins such as filaggrin 1, filaggrin 2, involucrin, and corneodesmosin, alongside lipids are indispensable for the formation of the cornified envelope.¹⁶⁶ Over the past two decades, filaggrin has garnered considerable attention due to its role in human AD. While filaggrin gene mutations are not observed in all individuals, they have been recognized as one of the most consistent genetic

predispositions for the development of AD.¹⁷¹ Loss-of-function mutations in filaggrin that lead to C-terminal protein truncations are significant predisposing factors in humans. In dogs, a subset exhibits reduced or undetectable epidermal filaggrin expression, as evidenced through immunofluorescence.¹⁷² Although filaggrin gene mutations have not been linked with canine AD across most breeds studied, a single-nucleotide polymorphism in the filaggrin gene was found to be strongly associated with AD in Labrador retrievers from the UK, highlighting a potential breed-specific and regional significance of filaggrin. Such insights may elucidate breed-specific phenotypes in canine AD.^{171,173,174}

In feline AD, the situation is more complex. Feline diseases with suspected allergic origins exhibit similarities to human atopic diseases and canine AD, but only to a certain extent. These allergic conditions in cats pose significant challenges for clinicians due to the diverse and non-specific reaction patterns exhibited by feline skin. Remarkably, the specific clinical manifestations of feline allergic diseases do not align completely with the characteristics of AD as defined in humans and dogs. This disparity suggests that while the term "atopic" may be applicable in describing certain allergic conditions in cats affecting the skin, respiratory, and gastrointestinal systems, these conditions do not consistently exhibit the same features as AD observed in other species.¹⁷⁵

Elevated gene expression of host defense peptides, particularly β -defensins and cathelicidin, has been observed in the skin of atopic dogs compared to healthy skin,¹⁷⁶ especially in the presence of active infection.¹⁷⁷ Intriguingly, this increase in gene expression does not consistently correlate with a similar increase at the protein level. These findings imply a potential dysregulation in the synthesis of host defense peptides in atopic skin.^{176,177} In addition, environmental factors and type 2 response can impact filaggrin expression and the development of atopic diseases. Increased humidity, sun exposure, and irritants can reduce filaggrin levels, leading to an acquired deficiency.^{178,179} Additionally, a Th2 inflammatory response in AD also reduces filaggrin synthesis.¹⁸⁰ This deficiency disrupts the skin barrier, allowing allergens, such as dust mites, pollen, and microbes to penetrate more easily, which enhances individual sensitization. Changes in the skin's physico-chemical properties further promote the growth of bacteria, such as *S. pseudintermedius*,¹⁸¹ and fungi, such as *Malassezia*,¹⁸² resulting in recurrent skin infections common in both human and canine AD patients.¹⁸³ The extensive variety of dog breeds and the challenges associated with gathering samples from significant numbers of both diseased and healthy animals within a specific geographic region could prolong the resolution of questions regarding filaggrin mutations, their impact on skin barrier and association with canine AD.¹⁸⁴

A genome-wide association study (GWAS) identified a 2.7 Mb genomic region on canine chromosome 3 (includes 37 genes) which is associated with AD in West Highland White Terriers.¹⁸⁵ Another study involving German Shepherd dogs pinpointed a genetic locus on canine chromosome 27.¹⁸⁶ Canine AD is considered a multifaceted disease, and GWAS for such diseases typically search for common variants across populations.^{166,185,187} However, it is possible

that the gene responsible for AD in a particular breed may be rare.¹⁸⁵ Although five breeds, Boxer, Bulldog, Labrador Retriever, Pug, and West Highland White Terrier, are globally recognized as predisposed to the condition, the prevalence of the disease still varies across different geographical regions and continents.¹⁸⁷ The distinctive expression patterns of microRNAs (short, single-stranded noncoding RNAs that regulate gene expression) were detected in dogs with AD, suggesting that the immunological mechanisms involved may be even more intricate.¹⁸⁸ Interestingly, an increased expression of miR215 was observed between healthy and AD dogs as well as non-lesional and lesional skin of atopic dogs suggesting an increased suppression of IL-17 receptor activation in canine AD.¹⁸⁸ These examples demonstrate the complexity of the disease, highlighting the influence of environmental factors and genetic makeup. Recently, the pet care product industry has seen considerable diversification and growth, becoming a significant market sector. Notably, many products available contain hazardous ingredients such as SLS/SDS and cocamidopropyl betaine. It is not unfounded to assert that regular exposure to these chemicals could potentially contribute to the development of diseases such as canine AD. In conclusion, there are many chemicals that negatively affect epithelial barrier regulation, including shampoos and cosmetic products developed for pets in recent years but the effects of these products on skin barrier needs further investigation.

4.4 | Micro- and nano-plastics

Micro- and nano-plastics are crucial pollutants that could persist in the environment with potential adverse health effects. Plastics have been widely found in various environments, such as oceans, lakes, rivers, wastewater treatment plants, soil, and even in the atmosphere. There are almost 9 billion tons of plastic produced in the world so far and approximately 1 billion tons are currently pollutants in nature. Given the decades long degradation times of plastics, it is expected that the problem will continue for many years to come as there is a vast amount of nondegradable plastic waste in nature. Synthetic substances found in the environment, particularly microplastics, can be ingested by a wide range of organisms, spanning from zooplankton to vertebrates.¹⁸⁹ Various sources can cause micro- and nano-plastics existence, including the breakdown of more oversized plastic items, industrial processes, and even microbeads in personal care products. In general, microplastics are plastic fibers, particles, and films with particle size <5 mm, including nanoplastics with diameter <0.1 µm.¹⁹⁰ They can easily penetrate tissues and interact with cells and cellular structural molecules. The human body is highly exposed to plastics even with intact epithelial barriers and membranes. It was demonstrated that micro and nanoplastics are present in various body fluids from whole blood to cerebrospinal fluid.¹⁸⁹ Moreover, the density of particles is influential on transfer rate and distribution in human body, in parallel with size. Several key mouse studies increased our understanding of the effects of microplastics on deep and relatively protected tissues. Polystyrene microspheres

or mixed plastics (5 µm) can traverse the gut barrier, move through the systemic circulation, and accumulate in remote tissues such as the brain, liver, and kidney in mice.¹⁹¹ It is important to note that microplastics and phthalates coexist in the environment and this combination may induce more detrimental influences. A recent investigation revealed that exposure to polystyrene alone slightly affects airway inflammation, and airway hyperresponsiveness, while co-exposure to polystyrene and di-(2-ethylhexyl) phthalate causes more significant damage in BALB/c mice. This combination results in increased oxidative stress and Th2 immune responses, and activation of the TRPA1 and p38 MAPK pathways.¹⁹² Polyethylene microplastics also reduce the proportion of CD4⁺ regulatory T and Th17 cells.¹⁹³ Interestingly, airborne microplastic and nanoplastic particles are both capable of modifying the nasal microbiota of mice, with microplastics exerting a more pronounced effect on the lung microbiota compared to nanoplastics. In this context, nasal *Staphylococcus* and lung *Roseburia*, *Eggerthella*, *Corynebacterium* are associated with both micro and nano plastic groups, suggesting they stand out as potential microbial biomarkers of micro- and nano-plastics-induced airway dysbiosis.¹⁹⁴ Furthermore, polystyrene microplastics together with dietary restriction treatment induce changes in the composition of the gut microbiota, which involve a decrease in the abundance of probiotics and an increase in the abundance of pathogenic bacteria in mice.¹⁹⁵

Given the various potential routes of microplastic exposure, it is highly likely that animals, similarly to humans, encounter these particles (Figure 1). Firstly, microplastics are present in the air, making direct inhalation a possible source of exposure for companion animals. While companion animals may commonly share water sources and certain foods with their owners, there may be notable distinctions in terms of oral exposure. Furthermore, contamination of food and water is common with both biodegradable and non-biodegradable plastics (Table 5). The presence of polyethylene terephthalate (PET) and polycarbonate has been shown in pet food.¹⁹⁶ Apart from being present in dog and cat food, plastics are also extensively used in the personal belongings of these animals. For instance, the majority of pet toys, chew sticks, dental products, and food/water bowls are manufactured from plastic materials. Given that a significant source of microplastics arises from particles breaking off or deteriorating from larger plastic objects, the use of plastic in pet products should be carefully considered. Indeed, these are important sources of microplastic ingestion by pets (Figure 3). The presence of microplastics characterized by the most common plastic polymer types, including polypropylene and PET, have been found in some postmortem samples of internal tissues (lungs, blood clots, kidney, ileum, and liver) from cats and dogs.¹⁹⁷ Farm animals are also exposed to microplastics through similar pathways. In this respect, the use of plastic mulch or silage packaging has the potential to contaminate fields, where grazing animals may ingest these plastics and subsequently release microplastics into the field through their feces.¹⁹⁸ A study on wild animals in Norwegian coasts found microplastics in the internal tissues, including stomach, intestine, liver, and muscle of otters, birds, and fish.¹⁹⁹ Another study has identified the microplastics

TABLE 5 The list of non-degradable/degradable plastics commonly used in human's and pet's life and their characteristics concerning structure and circularity potential. Food and water contamination by plastics is a growing environmental concern, as microplastics and harmful chemicals from plastic products infiltrate our ecosystems. These contaminants can leach into food and drinking water through packaging materials, agricultural runoff, and atmospheric deposition. Furthermore, pets, along with their toys and chew sticks, may be routinely exposed to plastic materials, such as polyamide, polypropylene, polyethylene.

Non-biodegradable plastics			Biodegradable plastics		
Polymer	Type	Circularity*	Polymer	Type	Circularity*
Polyvinyl chloride (PVC)	Petroleum-based	Nonrenewable Recyclable	Polyimide (PI)	Petroleum-based	Renewable Recyclable
Polyethylene (PE)	Petroleum-based	Nonrenewable Recyclable	Polyetherimide (PEI)	Petroleum-based	Nonrenewable
Polypropylene (PP)	Petroleum-based	Nonrenewable Recyclable	Polyglycolic acid (PGA)	Petroleum-based	Nonrenewable
Polystyrene (PS)	Petroleum-based	Nonrenewable Recyclable	Polyphenylene sulfide (PPS)	Petroleum-based	Renewable Recyclable
Polyamide (PA)	Petroleum-based	Nonrenewable Recyclable	Poly(vinyl alcohol) (PVOH)	Petroleum-based	Nonrenewable Recyclable
Polycarbonate (PC)	Petroleum-based	Nonrenewable Recyclable	Poly(lactic acid) (PLA)	Biobased	Renewable Recyclable
Polyoxymethylene (POM)	Petroleum-based	Renewable Recyclable	Thermoplastic starch (TPS)	Biobased	Renewable Recyclable
Poly(ethylene vinyl-coacetate) (EVA)	Petroleum-based	Nonrenewable	Polyhydroxyalkanoate (PHA)	Biobased	Renewable
Polyurethane (PU)	Petroleum-based	Renewable Recyclable	Polyhydroxybutyrate (PHB)	Biobased	Renewable
Biobased polyvinyl chloride (Bio-PVC)	Biobased	Renewable Recyclable			
Biobased polyethylene (bio-PE)	Biobased	Renewable Recyclable			
Biobased polypropylene (bio-PP)	Biobased	Renewable Recyclable			
Biobased polystyrene (Bio-PS)	Biobased	Renewable Recyclable			

Note: Reference:^{323, 324}

*Nonrenewable plastics are not sustainable for long-term application as they deplete with use. Renewable and recyclable plastics are crucial for advancing sustainable practices in the production and disposal of plastics.

even in the brain of wild fish.²⁰⁰ A more recent research has shown that tortoises frequently consume plastics in polluted anthropogenic areas of the Galapagos, highlighting significant health risks posed by plastics to tortoises and other wildlife.²⁰¹ Overall, there is significant data showing that almost all species worldwide are threatened by microplastics. Both, animals (wild and domestic) and humans will continuously face challenges as they are threatened by microplastics from their biosystems. This underscores the importance of recognizing the impact of particle pollution on sustainable development.

4.5 | Air pollution

Changes in air content have an inevitable impact in our ecosystem. Air pollution stands out as one of the key contributing factors for the increase in respiratory and other inflammatory diseases. It is responsible for 7 million deaths annually. Particulate matter (PM) is a

crucial component of air pollution, categorized based on its aerodynamic size. Of the global population, 99% reside in areas that surpass the threshold of annual air quality guidelines set by the WHO of less than $5 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$.^{202,203} In this context, fine particles with a diameter of $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) can penetrate deep into the lungs to alveolar levels and are associated with various health issues.^{12,202} $\text{PM}_{2.5}$ has the potential to impair the epithelial barrier by breaking down TJ proteins in both the upper and lower airways, reducing the expression of occludin and claudin-1, diminishing E-cadherin levels, lowering transepithelial electric resistance, and enhancing paracellular permeability.^{85,204,205} Exposure to $\text{PM}_{2.5}$ leads to oxidative stress, lysosomal membrane permeability, and lipid peroxidation as well as necrosis in airway epithelial cells and DNA damage.²⁰⁶ It may also cause impairment of the skin through DNA damage, persistent lipid peroxidation, protein carbonylation, and the depletion of structural epidermal proteins like cytokeratin, filaggrin, and E-cadherin in the skin's epithelial barrier.²⁰⁷⁻²¹¹ Similar to $\text{PM}_{2.5}$, PM_{10} also has

significant inflammatory and tissue-destructive effects on the respiratory tract. PM₁₀ can induce dysfunction in alveolar epithelial cells by reducing occludin levels at the plasma membrane and causing the dissociation of ZO-1, as observed in human and primary rat alveolar epithelial cells.²¹² Furthermore, PM₁₀ significantly increased mRNA expression and secretion of pro-inflammatory cytokines IL-6 and CXCL1 in mouse airway epithelial cells and it also induced the expression of IL-6, IL-8, and IL-1 β in human airway epithelial cells.²¹³ Livestock housing is a critical source of PM emissions. Levels of PM are highest in broiler houses compared with other animal species. On the other hand, the full impact of PM found in livestock housing, which may carry irritating gases, odors, and various microorganisms, remains unclear. When these elements attach to PM, they can intensify PM's biological effects, potentially increasing health risks. High concentrations of PM can threaten the environment, as well as the health and welfare of humans and livestock animals.²¹⁴

Natural sources, such as dust, sea salt, and forest fires, enhance air and aquatic PM, while anthropogenic sources like traffic, power plants, and industrial emissions contribute to the overall pollution load. As the usage of on-road vehicles has risen, diesel exhaust particulate (DEP) has become a significant component of air pollution (Figure 3). DEP is an intricate mixture of various compounds, found in both gaseous and particulate states.²¹⁵ The gaseous constituents within DEP encompass carbon monoxide (CO), nitrogen compounds, sulfur compounds, and a diverse range of low molecular weight hydrocarbons. These hydrocarbons include aldehydes, benzene, polycyclic aromatic hydrocarbons, and their nitro derivatives.²¹⁵ VOCs are organic molecules composed of carbon that possess a low boiling point, causing them to readily vaporize at room temperature, including benzene, toluene, and formaldehyde. These chemicals can be found in wallpapers, carpets, paints, plastics, and many cleaning products.^{216,217} When released into the air, these compounds can present health hazards. On the other hand, nitrogen dioxide (NO₂) and O₃ are critical gaseous components of air pollution. NO₂ is a prominent constituent of air pollution, particularly in the context of pollution originating from traffic sources. Exposure to NO₂, which deeply penetrates the lungs, is linked to an elevated risk of respiratory diseases, likely attributed to its potential to damage the epithelial barrier.^{11,12} In an animal model in New Zealand white rabbits, 3.0ppm of NO₂ exposure (24h in exposure chambers) caused a significant impairment of ciliary activity, mucociliary transport velocity, and epithelial permeability.²¹⁸ NO₂ and O₃ can reach high levels and be carried long distances by wind, spreading to rural areas. Ground-level O₃, a prominent constituent of photochemical smog, arises through sunlight-induced chemical reactions involving nitrogen oxides and VOCs discharged by sources such as motor vehicles, power plants, industrial boilers, refineries, and chemical plants.¹² Given that companion animals reside closer to ground level, this proximity could potentially expose them to an increased risk. Indeed, contamination from heavier particles near the ground may have a more direct impact on the health of companion animals due to their direct contact with these substances.

It is obvious that smoking also harms the animals living in the house, especially in smoking households. Cigarette smoke exposure

increases the number of inflammatory dendritic cells in the lungs and disrupts epithelial barrier function by suppression of pro-inflammatory cytokine and chemokine response.²¹⁹ It also strongly suppresses the antiviral immune response to influenza.²¹⁹ These interpretations also extend to other substances that contribute to indoor pollution. Indoor pollution exposure in companion animals has been demonstrated through the detection of cotinine, nicotine, and organohalogenated contaminants in their serum, urine, and hair.²²⁰⁻²²⁵ Exposure to household incense burning was significantly more common in dogs with respiratory disease compared to dogs without respiratory disease. In addition, cats suffering from respiratory disease were found in households with significantly higher PM_{2.5} concentrations than cats without respiratory disease.²²⁶ A remarkable relationship has been shown between indoor air pollution and canine AD.²²⁷ Exposure to indoor air pollution elicits the development of AD and the exacerbation of Canine AD Extent and Severity Index (CADESI-04). The mechanism through which indoor air pollution contributes to canine AD involves the elevation of TEWL and the initiation of an inflammatory response, ultimately resulting in the development of AD in dogs.²²⁷ The disruption of the epithelial barrier can facilitate the passage of numerous pathogens into deeper tissues and allow easier entry of allergen molecules into the airway parenchyma. Taken altogether, the consequences of air pollution are observed to play a role in the development of diseases in domestic animals, particularly companion animals, and can worsen preexisting conditions through the epithelial barrier impairment.

4.6 | Allergens

The impaired barrier protection caused by allergens can be attributed to the release of enzymes when allergens come into contact with the surface of the respiratory epithelium. Enzymes present in pollen and insect allergens can disrupt the barrier's ability to block substances from entering, making it easier for allergens to be absorbed (Box 4). This can initiate sensitization, marking the beginning of allergic reactions. These enzymes primarily target proteins involved in cell adhesion with E cadherin. They also impact receptors on cell surfaces like PAR2, which when activated triggers the release of cytokines such as IL-6 and IL-8.⁹ Protease inhibitors play crucial roles in maintaining lung homeostasis and they compensate for the impact of allergens and regulate apoptosis. Nonetheless, exposure to antigens results in varying expression levels of protease inhibitors, a phenomenon that takes place whether or not Th2 cytokines are present, causing damage to the lung epithelium.²²⁸ This indicates that allergic diseases have a detrimental impact on the epithelial barrier, leading to an escalation of the inflammatory profile and the exacerbation of disease progression in a self-reinforcing cycle (Figure 2).

The rise in urbanization and global warming has fostered a warmer and more humid environment, creating optimal conditions for the proliferation of house dust mites (HDM). The common building-construction style, characterized by non-opening windows, may also contribute to the issue. Various free-living mites that

BOX 4 Enzymes in allergen sources that could affect the epithelial barrier

- 1- Cysteine and serine protease: Major mite allergens (*Dermatophagoides farinea*-1 and *Dermatophagoides pteronyssinus*-1) and pollens (birch, ragweed, Kentucky blue grass, rye grass).³¹⁴
- 2- Serine protease and/or aminopeptidase: *Olea europaea*, *Dactylis glomerata*, *Cupressus sempervirens*, *Pinus sylvestris*.¹¹
- 3- Serine protease: *Aspergillus*, *Penicillium*.¹¹
- 4- Actinidin protease: Kiwi fruit.¹¹
- 5- Papain protease: Papaya.³¹⁵

inhabit human dwellings are termed domestic mites, including such taxa as HDMs (family Pyroglyphidae), storage mites (families Acaridae, Glycyphagidae and Chortoglyphidae) and their predator mites (family Cheyletidae).²²⁹ It is well known that *Dermatophagoides* genus is the most important cause of perennial allergic disease in both humans and companion animals.²³⁰ Furthermore, the best-characterized mites known to elicit IgE responses, in both humans and dogs are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. In humans, IgE antibodies targeting mite allergens demonstrate significant cross-reactivity, leading to reactions in the majority of individuals exposed to those mites.^{231,232} IgE antibodies against mites in dogs primarily target mite extract components with higher molecular weights. Here, it is important to acknowledge that the IgE response of dogs is different from that of humans regarding allergen profile to HDM. A significant proportion of dogs with AD have IgE specific for a *Dermatophagoides farinae* chitinase (Der f 15) of apparent molecular weight of 98 kDa.²³³ A 60 kDa *Dermatophagoides farinae* protein (Der f 18), with homology to chitinase, is a major allergen for humans and dogs sensitive to HDM.²³⁰ In house cats, HDM antigens (Der p 1, Der f 1 and group 2 allergens) were detected at a concentration of >2 mcg/g dust which is accepted as a risk factor for the development of sensitization in susceptible individuals.²³⁴ Both, clinically allergic cats and those with no clinical evidence of atopic disease showed the same concentrations of Der f-specific IgE, in contrast to specific pathogen-free cats.²³⁵ In addition, commercial dry foods may also be contaminated with storage mites, especially when kept in environmental conditions at higher temperature and humidity. Storage mites are another group of mites that often infest food sources, particularly grains. Commonly encountered storage mite species include *Acarus siro*, *Lepidoglyphus destructor*, *Glycyphagus domesticus*, and *Tyrophagus putrescentiae*. Notably, *Tyrophagus* mites can enter and proliferate in sealed food packages. It is critical to consider that contamination by storage mites could result in an incorrect diagnosis of food allergy in dogs sensitized to HDM.²³⁶

Sensitization of companion animals with AD to various plant-derived allergens is evident, including those from tree, grass, and

weed pollens. Similar to humans, a significant increase in the number of dogs and cats sensitized to grass pollen has been observed.²³⁴ An epidemiological study in Western France clearly demonstrated an increasing trend of dog sensitization to grass pollen, from 14.4% (1999 and 2002) to 27.7% (2007 and 2010). In this context, more than 80% of the 262 tests were positive for at least one allergen, and 21% to at least one pollen allergen.²³⁷ Concerning cats, sensitization was reported in 8.3% with asthma against orchard grass pollen, but only in 4% against birch pollen, and there were no reported cases of sensitization to ragweed or mugwort pollen.²³⁸ Furthermore, cats may occasionally develop rhinitis, which can provide opportunities to identify the specific pollen allergens responsible for their condition.²³⁴

Flea allergy is quite common in both dogs and cats. The clinical symptoms observed in a dog with a flea infestation can vary widely. However, the skin lesions and itching associated with flea allergy dermatitis (FAD) are predominantly located in specific areas, such as the lumbosacral region, the base of the tail, and the caudomedial thighs.²³⁹ It is important to note that a high flea count is typical in cases of flea infestation, but this may not necessarily be observed in dogs suffering from FAD. Furthermore, many dogs with atopic conditions might also experience concurrent FAD. This overlap can pose challenges in accurately diagnosing the specific allergic conditions affecting the dog.¹⁷³ Serum antibodies against flea antigens were isolated in dogs, revealing that up to 50% of dogs in flea-infested environments develop IgE antibodies against these antigens.²⁴⁰ Two key proteins, with molecular weights of 8–12 kDa and 40 kDa, were identified as significant in dogs. Additionally, an 18 kDa protein found in the saliva of cat fleas, *Ctenocephalides felis*, triggered reactions in 100% of dogs sensitized to fleas and 80% of clinically flea-allergic dogs.²⁴¹ Allergies to other insects are not very common in cats and dogs. Nevertheless, hypersensitivity reactions against *Hymenoptera*, *Aedes albopictus*, and tabanids are known. Intradermal tests indicate sensitizations to horse flies, *Culicoides* spp. (midges), *Simuliidae* (black flies) but also to other insects such as housefly, ant, deerfly, and mosquito.²³⁴ Indeed, the exact prevalence of allergies to stinging insects in pets is unknown, but some dog breeds, such as Bull Terriers, Boxers, and Staffordshire Terriers, may be more prone to severe reactions.²⁴²

Horses are susceptible to various allergic skin diseases, with insect bites being the predominant global trigger. The allergic reaction horses exhibit to bites from blood-feeding insects is currently known as Insect Bite Hypersensitivity (IBH). This condition is most commonly triggered by midges from the *Culicoides* genus (Diptera: Ceratopogonidae), although black flies from the *Simulium* genus (Insecta: Diptera: *Simuliidae*) are also known to cause reactions in some instances.²⁴³ IBH may also be linked with bronchial hyper-reactivity,²⁴⁴ reflecting a condition similar to the human atopic syndrome, which is characterized by both skin and respiratory symptoms.²⁴⁵ In horses, allergen hypersensitivity can lead to skin-related symptoms,²⁴⁶ such as eczema²⁴⁷ or urticaria,²⁴⁸ as well as respiratory issues including chronic coughing or recurrent airway obstruction.^{249,250} Horses also exhibit allergic symptoms

in response to environmental allergens such as HDM, molds,²⁵¹ and pollen.²⁵² The significance of the microbiome in equine health is also noteworthy. For instance; the respiratory microbiome of horses is varied, primarily composed of four phyla: *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*.²⁵³ However, a distinct difference has been observed between the bacterial communities in the lower respiratory tract of healthy horses and those with mild asthma, including a notable increase in *Streptococcus* in asthmatic horses.²⁵³ It is important to note that the role of the skin barrier in equine allergies, particularly in the pathogenesis of equine AD, remains largely unknown. Additionally, the potential for foods to trigger equine pruritus and AD is not well understood.²⁴³ In brief, there is limited mechanistic and experimental evidence-based information on skin barrier involvement regarding allergic skin diseases in horses.

Recently, food allergies have garnered increased attention and advancements in molecular-level understanding have been achieved in the allergology field. In fact, the origin of food allergy is quite complex, including genetic mechanisms, host immune response, environmental factors, and the epithelial barrier. The true prevalence and underlying mechanisms of food allergy in companion animals are largely unknown. In certain canine models, it is possible to measure an allergen-specific IgE response both during sensitization and after oral challenge. This indicates a potential involvement of IgE in the development of the disease.²⁵⁴ In dogs with adverse food reactions, the gene expression of Th1-, Th2-, and Treg-related cytokines in the duodenum remained similar to that of non-atopic dogs and did not exhibit any significant changes with dietary provocation. This implies that the intestinal mucosa may not be the primary site of T-cell activation responsible for the development of cutaneous food hypersensitivity.²⁵⁵ The dominant CD8⁺ T-cell characteristics and gene expression in the affected skin of dogs with adverse food reactions that were fed a novel protein home-cooked diet (consisting of ostrich, turkey, horse, or goat meat) for a minimum of 8 weeks remained unchanged, despite the resolution of clinical symptoms.²⁵⁶ Bovine serum albumin (ALB Bos d 6) and three egg white proteins [ovomucoid (Gal d 1), ovalbumin (Gal d 2), and ovotransferrin (Gal d 3)] were identified in the serum isolated from dogs with food allergies proven by a positive oral challenge. Furthermore, seven major chicken allergens (serum albumin, pyruvate kinase M, enolase 3, creatine kinase M, lactate dehydrogenase A, glyceraldehyde-3-phosphate dehydrogenase, and triose-phosphate isomerase) and one minor allergen (troponin C) have been identified to be relevant for dogs.²⁵⁷ Considering that most commercial pet foods contain chicken, it is a fact that there is a chronic exposure to antigens in companion animals with certain levels of chicken allergy.

Food allergy is well-recognized in both dogs and cats, serving as a crucial differential diagnosis in the evaluation of pruritic animals. It is a potential trigger for canine AD and may also coexist with feline atopic skin syndrome. Associated clinical manifestations in dogs include urticaria, recurrent pyoderma, and dorsolumbar pruritus, while in cats, symptoms may include urticaria, conjunctivitis, and respiratory issues. However, the etiopathogenesis and epidemiology

of these conditions are still not fully elucidated in companion animals.²⁵⁸

Dog-owner pairs exhibit simultaneous allergic traits, with a higher risk associated with urban environments, and they share some skin microbiota. This suggests that dogs and humans are predisposed to allergies due to similar risk factors. However, the absence of shared bacterial taxa that predispose to or protect from these allergies implies that factors other than environmental microbial exposures could influence the differences, possibly because furry dog skin and furless human skin select different microbial taxa.²⁵⁹

The widespread use of antibiotics has been linked to a higher risk of allergy development.^{260,261} Specifically, prenatal and early life exposure to antibiotics has been associated with an increased risk of developing AD and food allergies.^{260,262} The connection between antibiotics and allergies is further supported by evidence suggesting that antibiotic use, particularly in early life, can disrupt the intestinal bacteria that regulate IgE production, potentially leading to allergic diseases.²⁶³ Notably, oral administration of *Streptococcus thermophilus* (ST218) has been shown to alleviate allergic responses in mice treated with antibiotics, primarily through the modulation of mucosal and systemic responses rather than the restoration of the intestinal microbiota.²⁶¹ Early exposure to some probiotics can have both short-term and long-term effects on dogs with AD.^{264–267} Regarding canine gut microbiota, a recent study supports earlier findings from human research, demonstrating that antibiotics, gut microbiota, and atopic manifestations are interconnected.²⁷ The severity of symptoms was positively associated with antibiotic usage, which, in turn, affected the microbiota composition. The microbiota diverged between atopic and healthy individuals, likely due to lifestyle differences such as the frequent use of antibiotics in atopic dogs. *Escherichia-Shigella*, enriched by antibiotic use, has emerged as a potential candidate contributing to atopy, warranting further investigation in experimental setups.²⁷ A reduction in skin microbiome diversity and a dominance of *Staphylococcus* are characteristic of atopic flares. In addition, with the growing antibiotic resistance of *Staphylococcus* presenting substantial challenges, there has been a necessary pivot toward using topical therapies instead of broad-spectrum antibiotics. This shift highlights the vital importance of fostering a diverse and sustainable microbiome.²⁶⁸

The concept of the balance between eubiosis/dysbiosis continues to evolve, encompassing alterations in the diversity and structure of the microbiome, as well as functional changes such as variations in the production of bacterial metabolites.²⁶⁹ Concerning feline skin microbiome, the dominant bacterial phyla identified are *Proteobacteria*, *Bacteroidetes*, *Firmicutes* (which include *Staphylococcus* species), *Actinobacteria*, and *Fusobacteria*.²⁷⁰ The mycobiome predominantly consists of *Ascomycota*, which are largely soil-borne fungi. Additionally, there is a notably lesser quantity of *Basidiomycota*, which includes various yeast organisms like *Malassezia* species.^{271,272} Independent of their health status, feline skin supports diverse staphylococcal communities, including *Staphylococcus capitis*, *Staphylococcus epidermidis*, and *Staphylococcus felis*.²⁷³ Although both healthy and allergic cats harbor similar staphylococcal species,

certain species are more prevalent in healthy cats compared to their allergic counterparts. In healthy feline samples, the majority of staphylococcal sequences have been identified as *S. epidermidis*, whereas *S. capitis* has been the most prevalent species in samples from allergic felines.^{272,273} Furthermore, cats with allergies, cornification defects, and endocrinopathies, which show a predisposition to yeast overgrowth, exhibit parallels to canine patients suffering from *Malassezia dermatitis*.²⁷⁴ Similar abundances of bacterial taxa may be observed across the skin microbiota of both allergic and healthy dogs. Notably, taxa minimally present in healthy dogs are often absent in allergic ones. In a comparative study of healthy and allergic dogs, a significant observation was the considerably reduced prevalence of *Ralstonia* spp. in allergic dogs, which was less than 0.02% across samples, except for one axillary sample, where it constituted 45%. Various other bacterial genera, including *Bacillus* spp., *Sphingomonas* spp., *Mycoplasma* spp., and *Staphylococcus* spp., showed differing prevalences depending on the body area sampled, such as the axilla, groin, interdigital skin, and nostrils.²⁷⁵ It is important to note that the *Cutibacterium* genus is prevalent in the healthy skin microbiota, where it significantly contributes to skin homeostasis and wards off harmful pathogens, notably through the mechanism of reducing pH levels.²⁷⁶

In healthy dogs and cats, the gastrointestinal tract microbiota is typically characterized by the prevalence of *Firmicutes* and *Bacteroidetes* as the dominant phyla. Moreover, *Fusobacteria*, *Proteobacteria*, and *Actinobacteria* are notable components of this microbiota.^{277–280} *Fusobacterium* is linked to IBD and colorectal cancer in humans,²⁸¹ but there is no apparent association with non-IBD dog samples. In dogs, substantial quantities of *Fusobacterium* have been observed in the digestive tracts of healthy individuals who consume a BARF diet^{280,282} and more access to the outdoors.²⁸³ An essential aspect to highlight is the interspecies interactions, including the well-documented and substantial bond between pet owners and their pets, which may influence microbiota dynamics. Children living with dogs showed a distinctive gut microbiota composition compared to those without dogs. Interestingly, this was characterized by a higher abundance of *Bacteroides* and short-chain fatty acid producing bacteria like *Ruminococcus* and *Lachnospiraceae*. Administering probiotics to dogs influenced the gut microbiota composition of both dogs and children, leading to a notable decrease in *Bacteroides* levels.

The lung microbiota of healthy dogs consists of a microbial community that is akin to that observed in healthy humans, with major phyla including *Firmicutes*, *Actinobacteria*, *Proteobacteria* and *Bacteroidetes*.^{284,285} Here, it should be noted that factors such as breed and living conditions significantly influence the lung microbiome.²⁸⁵ It has been observed that with the development of disease in cats and dogs, serious changes and shifts to certain phyla occur in the microbiome. To give an example, the lung microbiota of healthy cats is typically dominated by the phylum *Proteobacteria*. In cats with asthma and chronic bronchitis, there is a notable change in the lung microbiota composition, transitioning from being predominantly *Proteobacteria* towards *Bacteroidetes* as the diseases progress.²⁸⁶ In addition, a novel *Filobacterium* species, *F. felis*, has been associated

with chronic bronchitis in cats, indicating a potential pathogenic role.²⁸⁷

Available scientific information on canine and feline allergology is quite limited compared to human studies. Thus, there is a high need for future research into allergies in companion animals. From the epithelial barrier theory aspect, given the close coexistence of companion animals and humans, here, we postulate that animals are similarly exposed to allergens, potentially experiencing shared adverse effects which may extend to allergic diseases. Further studies to support these findings are warranted.

4.7 | Genetic structure changes, breed factor, and diversity in companion animals

In comparison to humans, one of the most significant biological distinctions in domestic animals, which can profoundly influence genetic and cellular mechanisms, is the rigorous selection process animals undergo. Selection focused on high productivity in farm animals has allowed the development of many different breeds. In pet animals, this process can be a selective breeding procedure or can be shaped entirely to achieve the desired appearance. This intensive selection has led to incredible morphological variation, especially in dogs, from the Miniature Pinscher to the Great Dane, from the Bulldog to the Greyhound. Humans began the domestication of dogs over 15,000 years ago, originating from two ancestral populations of extinct grey wolves in various regions globally. This process of domestication coincided with the co-evolutionary history of these two species.²⁸⁸ The global spread of dogs resulted in population bottlenecks, selective pressures, and gene flow among different dog populations, ultimately leading to genomic and phenotypic changes.¹ Recent evolutionary studies have shed light on the domestication process of cats, revealing that contemporary cats are the outcome of two significant ancestral cat lineages.²⁸⁹ While the range of body sizes in cats remains relatively limited compared to dogs, there is a wide variety of cat breeds, from British Shorthairs to Siamese cats, that have been developed over the years. Certainly, the biological consequences of this extensive process of selection in cats and dogs extend beyond physical appearance. The genome is a very dynamic structure and many gene interactions such as epistasis and pleiotropy can cause selection not only to be limited to desired traits but also to changes in many biological characters that cannot be predicted through indirect selection. On the other hand, inbreeding depression leads to a loss of biological fitness. In closed populations, such as pedigree dogs and cats, a degree of inbreeding is unavoidable. However, it is crucial to study the patterns of inbreeding that may impact the health and fitness of both individuals and the population as a whole.²⁹⁰ In other words, decreased genetic variability through intense inbreeding is associated with impairment of many vital features from developmental disruption to the reduction in immune system functions.^{1,291–295} Importantly, the decrease in immune system functionality results in a higher susceptibility to infectious diseases and cancer.²⁹⁶

At first glance, it might appear that cesarean sections would be unnecessary in dogs except for pathological cases. However, breeds with extreme skull shapes or sizes that have been selectively bred in recent decades to emphasize specific traits, known as “over-typed” conformations, rely on human interventions for their continued existence. Certainly, in English Bulldogs, as well as other brachycephalic breeds, the size of the fetus's head is too large to pass through the female dog's pelvis, making cesarean section necessary in 94% of all deliveries.^{1,297} Considering that abnormal immune system maturation is associated with nonvaginal births, selection based on physical appearance may cause events that may change the lives of animals in their later ages. Furthermore, intense selection for a desirable trait can obscure unforeseen consequences resulting from the phenomenon of genetic linkage, which is influenced by the location of genes on chromosomes. The most prevalent inherited conditions are allergic skin diseases, with AD in Labrador Retrievers exhibiting a heritability rate of 47%, while in German Shepherds, it is linked to a specific region on chromosome 28.^{1,186}

Brachycephalic dogs not only suffer from brachycephalic obstructive airway syndrome (BOAS) but are also commonly seen by veterinary dermatologists for skin issues, with English Bulldogs and Pugs being especially affected. Structural changes linked to brachycephaly, which result in skin folds and ear canal constriction, along with documented primary immunodeficiencies in certain breeds, increase the likelihood of pyoderma, *Malassezia dermatitis*, and external/middle ear infections.²⁹⁸ Skin fold dermatitis, or intertrigo, is a serious problem in brachycephalic breeds, especially in British Bulldogs, French Bulldogs, Pugs, Pekingese, Boston Terriers, and Shar Peis.^{299–306} Ichthyosis is a rare genetic disease which is caused by a mutation in *NIPAL-4* (nipa-like domain-containing 4) leading to abnormal lipid metabolism in the epidermis. Cavalier King Charles Spaniels and American Bulldogs have been reported to show predisposition to this disease.^{298,307–311}

Predisposition can also be observed in some other diseases, including congenital alopecia (French bulldog, Lhasa Apso, and Chihuahua), tyrosinase deficiency (Chow chow), cutaneous asthenia (Boxer), canine flank alopecia (Boxer and Affenpinscher), follicular dysplasia (Chihuahuas, Yorkshire Terriers, Shih Tzus, Boxers, Boston Terriers, Cavalier King Charles Spaniels, and blue Chow Chows).²⁹⁸ German shepherd, Labrador Retriever, West Highland White terrier, Boxer, Rhodesian Ridgeback, and Pug breeds are predisposed to developing adverse food reactions.^{88,254} As a counterpart to celiac disease in humans, gluten sensitivity has been investigated in dogs, potentially leading to gastrointestinal symptoms in specific breeds, including Irish Setters and Soft Coated Wheaten Terriers. In some breeds, non-gastrointestinal diseases (e.g., movement disorders and gall bladder mucocoele) are linked to gluten sensitivity, such as Border Terriers.⁸⁸ On the other hand, Siamese cats or Siamese cross-breeds seem to be at an increased risk of developing food allergy.²⁵⁴ Due to genomic dynamics and reduced genetic diversity in pet animals subjected to intense selection, these existing conditions may have more serious effects (Figure 3). Moreover, from the perspective of the epithelial barrier theory, it may partially explain why diseases are more common in these breeds.

5 | CONCLUSION

Domestic animals, particularly pets, coexist within the same living environment as humans. However, compared to human medicine, there are relatively limited experimental studies in veterinary science. Changes in environmental factors, and thus, in the exposome are related to the increasing prevalence of epithelial barrier-related diseases, especially in companion animals. Notably, there is a need for further research in this subject. However, current data emphasize the need to pay urgent attention to some areas. Additives such as taste enhancers and emulsifiers, pollution, micro- and nanoplastics, various allergens, detergents, and surfactants pose serious threats to both domestic animals and humans. Pets are exposed to these factors indirectly by sharing environments with humans, and directly through products such as canned food, pet shampoo, toothpaste, and treats. The quality and quantity of additives in food as well as the chemicals utilized in other pet products require more efficient monitoring. In particular, some additives that are banned in humans still continue to be used in animal foods. Serious restrictions or bans should be enforced on these and related matters. In addition, consumers and pet owners should reduce their purchase and use of such products. The epithelial barrier theory provides insights into the mechanisms for the pathophysiology of various diseases and it also leads to novel strategies for diagnosis, treatment, and prevention of diseases related to epithelial barrier leakiness. It also encompasses all previously proposed mechanisms and offers a compelling explanation for the abrupt surge in chronic non-communicable inflammatory diseases witnessed over the past six decades, making it highly applicable in veterinary medicine.

Critically, there is a need for a worldwide strategy to address concerns such as environmental pollution and microplastics, posing threats to the well-being of both humans and animals. In this One Health context, addressing these increasing environmental challenges requires global collaboration and the combined efforts of all available resources. The challenges include uncooperative government institutions, public resistance, infrastructure deficiencies, and poverty, all hindering effective action. Strategies to mitigate diseases linked to a disrupted epithelial barrier involve avoiding and controlling the use of these products, developing safer alternatives, identifying biomarkers for leaky barriers, enhancing tissue-specific barrier molecules, blocking bacterial translocation, preventing opportunistic pathogen colonization, and implementing dietary and microbiome interventions. Furthermore, many questions remain to be solved concerning molecular dynamics, such as the epigenetics regulation mechanisms in the context of concomitant intervention of environmental factors. Evaluating the challenges posed by the climate crisis, pollution, energy management, and biodiversity conservation is crucial, and it is equally vital to enforce and oversee sustainable approaches.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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