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Review – One Health

Thymomodulin as an Immunomodulatory Agent in Animal Species: a Scoping Review on Animal Health Impacts, One Health Interfaces, and Translational Relevance

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HIGHLIGHTS

- Thymomodulin modulates innate and adaptive immunity across animal species.
- Thymomodulin enhances vaccine response, disease resistance, and outcomes.
- Thymomodulin use in animals could indirectly reduce antimicrobial use and zoonotic risk.
- Evidence is heterogeneous; standardized studies are required for validation.

Abstract: Thymomodulin is a thymus-derived peptide preparation with immunomodulatory properties studied in experimental and veterinary contexts. Within a One Health framework, integrating animal, human, and environmental health, enhancing animal immunity is hypothesized to aid disease prevention, reduce zoonotic transmission, and decrease antimicrobial use. This scoping review mapped evidence on thymomodulin and comparable calf thymus extracts as immunomodulators in non-human animals from 2000 to 2025, evaluating their relevance for One Health strategies. A structured literature search (1 January 2000-31 December 2025) was conducted in PubMed, Scopus, Web of Science, and SciELO, supplemented by grey literature and patent searches. Peer-reviewed studies reporting immunological or clinical outcomes in non-human animals

were included; human-only studies and those lacking immune or health endpoints were excluded. Across species, thymomodulin consistently modulated innate and adaptive immunity. In fish, dietary supplementation enhanced vaccine responsiveness, antibody titers, and survival after pathogen challenge. In rodents, thymomodulin restored immune function in immunosuppressed models and accelerated pathogen clearance. In companion animals, adjunct therapy improved clinical outcomes, including increased survival and faster remission in cats with disseminated sporotrichosis, as well as improved hematological parameters in immunocompromised animals. Evidence from poultry and swine suggests enhanced vaccine-induced immunity and maternal transfer of immune protection. Overall, thymomodulin acts as an immune normalizer, reinforcing host defenses under immune compromise. These immunological benefits could potentially reduce pathogen shedding and the need for antimicrobials indirectly; however, the evidence remains heterogeneous. Standardized clinical trials and field-based studies are needed to support translation into One Health practice.

Keywords: Thymomodulin; Immunomodulation; Animal Health; One Health; Immune Response; Veterinary Immunology.

INTRODUCTION

Thymomodulin is a purified acid lysate of calf thymus glands rich in peptides below 10 kDa that exert immunoregulatory effects [1–3]. As a thymus-derived product, thymomodulin mimics thymic hormones that regulate T-lymphocyte maturation and immune homeostasis. It exhibits dual myelopoietic and immunomodulatory activity, with the capacity to stimulate bone marrow progenitors and modulate both B- and T-lymphocyte functions, thereby enhancing innate and adaptive immune responses [4,5]. Unlike some thymic derivatives, thymomodulin retains biological activity after oral administration, supporting its practical application in experimental and clinical settings [2,6]. Over the past decades, thymomodulin and related calf thymus extracts, such as TFX®, have been investigated as therapeutic agents for recurrent infections, immunodeficiencies, and as adjuncts to vaccination or anticancer therapies [7,8]. While human trials reported benefits in respiratory infections and during chemo- or radiotherapy [3], increasing attention now focuses on veterinary and preclinical contexts. These findings support the concept that biological compounds can interact with host defense mechanisms and influence susceptibility to infection and treatment response [9,10].

Experimental and applied studies show that thymomodulin influences immune function across multiple animal species. In aquaculture, dietary supplementation enhanced vaccine responsiveness, increased specific antibody titers, and improved survival following pathogenic challenge [1]. In laboratory rodents, thymomodulin and related thymus extracts restored immune function in immunosuppressed models and accelerated pathogen clearance, including improved elimination of helminth parasites [2,5]. In companion animals, thymomodulin served as an adjunct therapy improving clinical outcomes; for instance, in cats with disseminated sporotrichosis, thymomodulin substantially increased survival and hastened lesion remission [2], while improved body condition and recovery emphasized immune status as a key prognostic factor [6,11]. Additional studies reported elevated immunoglobulin levels (IgG, IgA) and normalization of hematological profiles in immunocompromised animals such as FeLV-infected cats, supporting a broad immunostimulatory profile [7,12].

These effects are particularly relevant within the One Health framework, which recognizes the interdependence of animal, human, and environmental health. Strengthening immune competence in animals may reduce infectious disease burden, decrease pathogen shedding, and lower the risk of zoonotic transmission to humans [7,11,13]. In feline sporotrichosis, enhanced immune control benefits the animal and potentially reduces environmental and human exposure to *Sporothrix* spp. [11]. In agricultural systems, improved herd or flock immunity may limit amplification of zoonotic agents such as *Salmonella*, *Campylobacter*, or emerging coronaviruses. Enhanced immune resilience may also reduce the need for prophylactic or therapeutic antimicrobial use, supporting antimicrobial stewardship and mitigating resistance in veterinary and human medicine [14]. Experimental studies further demonstrate that non-antibiotic compounds can enhance antimicrobial efficacy when combined with conventional drugs, as shown by the synergistic interaction between ascorbic acid and antibiotics against *Pseudomonas aeruginosa* [15]. In this context, thymomodulin represents a promising immunomodulatory tool at the animal–human–environment interface, illustrating how integrated approaches can improve infection control while potentially reducing selective pressure for antimicrobial resistance.

To our knowledge, no study has explicitly examined thymomodulin within a One Health framework. A comprehensive search of scientific literature and repositories did not identify any article integrating thymomodulin into the animal-human-environment health triad or clearly positioning this immunomodulator

within a One Health conceptual or analytical context in publicly accessible databases. This absence is notable given the expanding use of One Health approaches in the study of zoonoses, antimicrobial resistance, and environmental determinants of health.

Available evidence remains fragmented and indirect. Some studies evaluated thymomodulin as an adjunct to antifungal therapy in cats with disseminated sporotrichosis, a zoonotic disease of high One Health relevance. Veterinary and public health publications have emphasized One Health strategies for feline sporotrichosis and other zoonoses, yet thymomodulin is not considered part of these strategies. Other experimental and clinical studies described the immunomodulatory effects of thymomodulin without reference to One Health principles [9,10,15]. Occasional mentions in theses or grey literature associate thymomodulin with animal health and broadly cite One Health, yet none provide a conceptual, empirical, or integrative analysis of thymomodulin within this paradigm.

This clear disconnect between the expanding One Health literature and the growing body of research on thymomodulin defines a substantive gap in the field, limiting systematic understanding of whether and how thymomodulin could contribute to disease prevention, zoonotic risk reduction, antimicrobial stewardship, and environmental health. The present scoping review addresses this gap by situating thymomodulin within a One Health framework and mapping the available evidence from 2000 to 2025 on thymomodulin and comparable calf thymus extracts as immunomodulators in non-human animals, emphasizing species, health conditions, intervention characteristics, immune and clinical outcomes, and One Health relevance. Academic databases (PubMed, Scopus, Web of Science, SciELO), grey literature sources (Google Scholar, OpenGrey, institutional repositories, conference proceedings), and clinical trial registries (ClinicalTrials.gov, WHO ICTRP) were searched for publications from 1 January 2000 to 31 December 2025 using combinations of the keywords thymomodulin, thymus extract, calf thymus, immunomodulator, animal species (fish, rodents, cats, dogs, livestock), and contexts such as infection, vaccination, immunosuppression, and One Health. Peer-reviewed studies in non-human animals reporting immune-related or health outcomes after thymomodulin or similar thymus extracts were included; studies without immunological endpoints or restricted to humans were excluded. Data extracted included species, health condition, study design, setting, intervention characteristics, comparators, immune outcomes, clinical or vaccine-related outcomes, reported limitations, and evidence gaps. Results are presented as a descriptive synthesis organized by major animal categories, followed by a summary mapping table.

MATERIAL AND METHODS

This study was conducted as a scoping review to map the breadth, characteristics, and distribution of evidence on thymomodulin and comparable calf thymus peptide extracts as immunomodulators across non-human animal species. Methods and reporting followed the PRISMA extension for Scoping Reviews (PRISMA-ScR) to support transparency and reproducibility [16], and the overall methodological approach was aligned with the Joanna Briggs Institute (JBI) guidance for scoping reviews, including the sequential steps of defining the question, identifying evidence, selecting sources, charting data, and collating and summarizing findings [17]. The study selection process is summarized in the PRISMA-ScR flow diagram (Figure 1), which details the number of records identified, screened, excluded (with reasons), and included in the final synthesis, in accordance with PRISMA-ScR recommendations. A protocol describing the planned methods was prepared *a priori*, and it has now been retrospectively registered in the Open Science Framework (OSF, registration link: https://osf.io/vtc6b) during the revision phase of the manuscript to enhance transparency. This retrospective registration, completed after the initial study, does not compromise the methodological integrity or transparency, as the publicly available protocol reflects the procedures that were actually implemented.

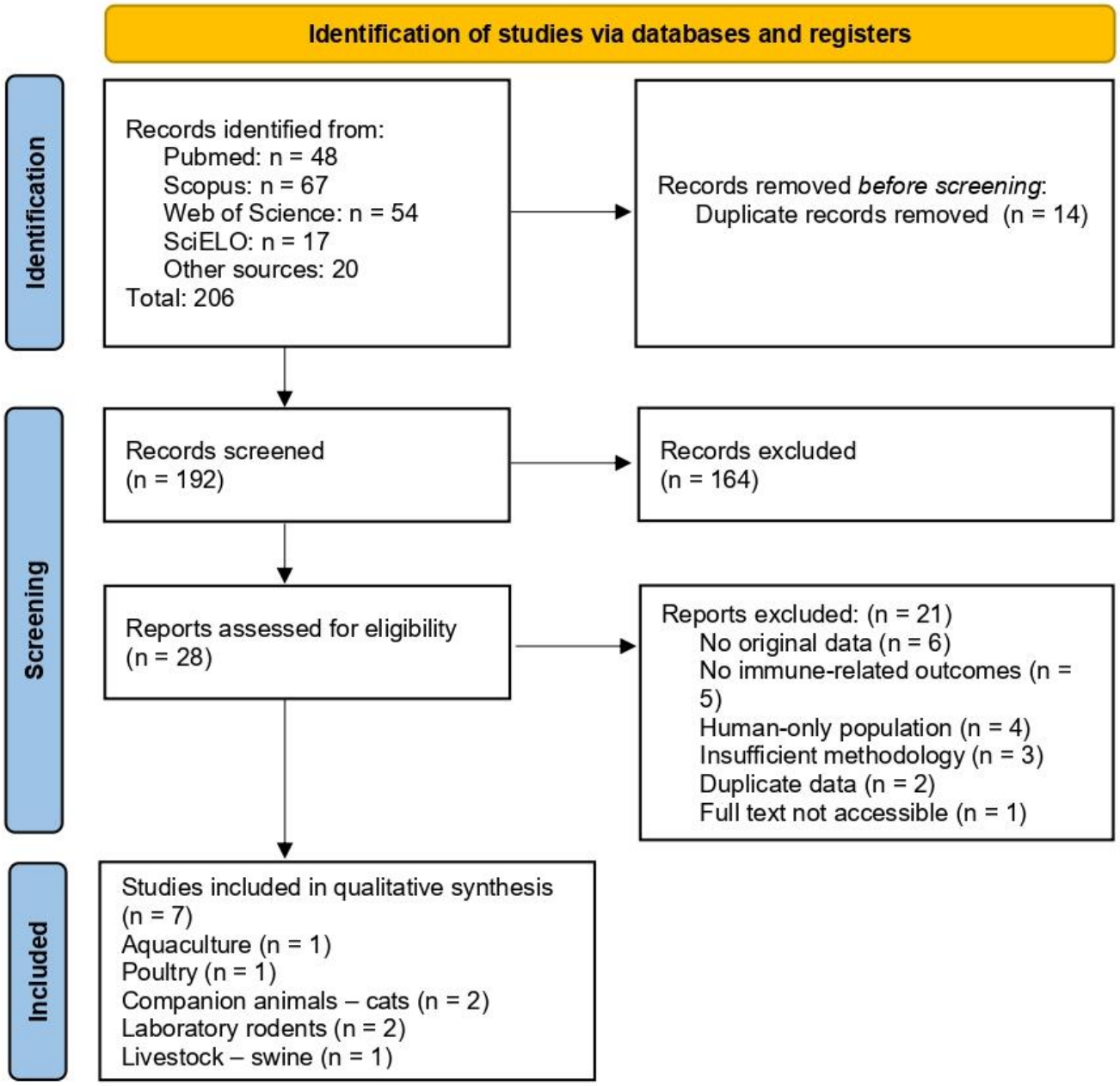

Figure 1. PRISMA-ScR flow diagram of the study selection process.

The review objective was to map and describe evidence on the immunomodulatory effects of thymomodulin or equivalent calf thymus preparations in animals, with emphasis on outcomes that can inform One Health interfaces such as vaccine performance, host resistance, and disease contexts with translational or zoonotic relevance. Eligibility was defined using the JBI Population, Concept, and Context framework [17]. The Population included any non-human animal species. The Concept encompassed thymomodulin and comparable thymus-derived peptide extract interventions and their effects on immune function or health outcomes. The Context included veterinary, preclinical, and translational research settings, explicitly considering implications that link animal health to broader One Health priorities. Eligible sources comprised peer-reviewed articles and relevant grey literature published from 1 January 2000 to 31 December 2025, reporting immunological, clinical, or vaccine-related outcomes in treated animals and using experimental or observational designs, with full texts available in English. Exclusions comprised human-only studies, reports lacking immunological or health outcomes, publications without original data (unless uniquely reporting otherwise unavailable data), and studies not accessible in full text or not published in English.

A comprehensive search strategy was developed to capture both indexed and non-indexed (grey) literature. Electronic searches were performed in PubMed, Scopus, Web of Science, and SciELO using

controlled vocabulary (where available) and free-text terms for thymomodulin and thymus extracts, paired with immunomodulation-related terms and animal-related terms, combined with Boolean operators to maximize sensitivity. Searches were limited to the predefined 25-year window through 31 December 2025. To reduce retrieval bias and improve coverage beyond traditional databases, additional searches were conducted in Google Scholar, OpenGrey, and institutional repositories to identify dissertations, theses, and reports; relevant veterinary and immunology conference proceedings were also checked when accessible. Clinical trial registries (ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform) were screened for ongoing or unpublished studies involving thymomodulin or thymus extracts in animals. Reference lists of included sources were examined to identify additional eligible records. All searches were conducted with the support of an experienced librarian. Retrieved records from all sources were merged and de-duplicated using reference management software before screening.

Study selection followed a dual-reviewer process to minimize bias. Two reviewers independently screened titles and abstracts against the eligibility criteria, then assessed the full text of records deemed potentially relevant [18]. Discrepancies were resolved by discussion and consensus, with a third reviewer consulted if needed to reach a final inclusion decision. The selection process is documented in a PRISMA-ScR flow diagram, summarizing the number of records identified, removed as duplicates, screened, evaluated in full text, and included.

Data charting was performed using a standardized extraction form designed to capture study characteristics and One Health–relevant information. For each included source, charted items included the animal species and key population descriptors, study design and setting, intervention details (thymus extract type, dose, regimen, and route of administration), and all reported immunological, clinical, or vaccine-related outcomes (e.g., immune cell counts or functions, antibody levels, cytokine changes, clinical recovery metrics). Any explicit discussion of One Health relevance, such as implications for zoonotic disease control, antimicrobial use, or cross-species translational value, was also recorded. Two reviewers independently charted data from the sources and then compared their entries for consistency, resolving any differences by consensus. We did not contact authors for additional information, so charting relied on data as reported in the sources.

Synthesis of results was descriptive and qualitative, following a narrative approach. Given the diversity of species and study designs, no quantitative meta-analysis was performed. Instead, evidence was organized by major animal groupings (aquatic species, laboratory rodents and models, companion animals, and livestock) to highlight patterns, heterogeneity, and knowledge gaps relevant to One Health considerations. Within each category, we summarize the contexts (e.g., disease models, clinical conditions), the effects of thymomodulin on immune parameters and health outcomes, and any noted limitations. A summary mapping table is provided to give an overview of key studies and findings.

RESULTS

Aquaculture Species (Fish)

Studies in aquaculture have primarily examined thymomodulin as a dietary immunostimulant to enhance disease resistance and vaccine efficacy in fish. Only a limited number of investigations have evaluated thymus-derived immunomodulators in this context, with Nile tilapia (*Oreochromis niloticus*) serving as the main experimental model. Salvador and coauthors (2022) [1] conducted a controlled trial in which tilapia received feed supplemented with 0.3% thymomodulin for 30 days prior to vaccination with an inactivated *Streptococcus agalactiae* bacterin, a major pathogen in tilapia farming [1]. Fifteen days post-vaccination, fish were challenge-infected with virulent *S. agalactiae* to assess protection. Fish receiving thymomodulin exhibited significantly higher specific antibody titers at 14 and 21 days post-infection and substantially better survival after challenge compared with vaccinated controls without thymomodulin [1]. Remarkably, thymomodulin-supplemented groups achieved greater protection than vaccination alone, and even unvaccinated fish receiving thymomodulin showed higher resistance than vaccinated fish without supplementation, suggesting that thymomodulin enhanced both baseline innate immunity and vaccine-induced adaptive responses [1].

These findings indicate that thymomodulin can augment vaccine efficacy in fish, likely through combined effects on humoral immunity and innate defense mechanisms such as phagocytic activity and leukocyte function, although detailed mechanistic studies in fish remain limited [1]. No adverse effects on growth performance or behavior were observed at the tested inclusion level of 0.3% of feed. Broader aquaculture and immunonutrition literature supports that immunostimulants, including thymus extracts, can activate fish immune defenses, improve survival under stress, and correlate with higher leukocyte counts and antibody

levels, potentially reducing antibiotic use by preventing infectious outbreaks. Field observations also associate immunostimulant supplementation with improved growth and survival under challenging farming conditions [14].

Although evidence on thymomodulin in aquaculture remains limited to a few experimental studies and a single host–pathogen model, the tilapia vaccination study provides proof of concept that thymomodulin can serve as an effective adjunct to vaccination. By strengthening immune competence and improving disease resistance, such interventions may contribute to reduced antimicrobial use and lower production losses, aligning with One Health goals of antimicrobial stewardship and sustainable food production. Nevertheless, the existing evidence is constrained by its focus on one species and one disease under experimental conditions, highlighting the need for field studies across diverse aquaculture systems, multiple fish species, and infectious contexts to establish the generalizability and practical impact of thymomodulin in fish health management.

Laboratory Animals (Rodents and Other Models)

Experimental models in laboratory rodents, primarily mice and rats, have been central in elucidating the immunomodulatory actions of thymomodulin and related calf thymus extracts such as TFX. A substantial body of preclinical research demonstrates that these thymic peptides can correct immune imbalances across diverse induced conditions and immune challenges. In vitro, thymomodulin stimulates the phagocytic and bactericidal activity of macrophages and neutrophils [3], while in vivo it promotes T-cell maturation and lymphocyte responsiveness in both normal and immunosuppressed animals [4,6]. In models of secondary immunodeficiency, including protein–calorie malnutrition, pharmacological immunosuppression, thymectomy, and stress-induced immune suppression, thymus extracts restore thymus and spleen cellularity, normalize leukocyte counts, and reconstitute T-cell proliferative responses to mitogens [2,3,6,19]. Oral thymomodulin restored mucosal immunity in protein-deprived Wistar rats, as evidenced by increased numbers of IgA-producing cells in gut-associated lymphoid tissue [19]. In mice treated with cyclophosphamide or high-dose corticosteroids, thymomodulin or TFX accelerated recovery from leukopenia and normalized antibody responses to antigenic challenge. Thymus extract also reversed suppression of T-cell proliferation and antibody production induced by restraint stress, indicating that thymic peptides counteract stress hormone–mediated immunosuppression [2].

Animal infection models provide further evidence that thymomodulin enhances disease resistance. In parasitic infections, particularly *Trichinella spiralis*, thymomodulin and TFX increased inflammatory cell infiltration at infection sites, reduced muscle larval burdens, and accelerated parasite clearance compared with untreated controls [5]. Studies documented higher leukocyte accumulation around encysted larvae, increased apoptotic lymphocytes within infected tissues, and significantly fewer viable parasites, suggesting immune-mediated enhancement of parasite elimination. In bacterial infection and sepsis models, thymus extracts improved survival when administered alongside conventional antimicrobials; mice challenged with lethal *Escherichia coli* or *Staphylococcus aureus* infections showed prolonged survival with combined antibiotic and thymus extract treatment versus antibiotics alone, likely reflecting priming of innate defenses [5].

Thymic extracts also exhibit immunomodulatory effects in non-infectious models. In experimental allergic encephalomyelitis (EAE), early studies in chickens reported modest reductions in inflammatory markers, whereas later work in rats demonstrated that intramuscular thymus extract or active peptide fractions markedly reduced clinical severity and improved spinal cord histopathology. In tumor-bearing mice, thymus extracts mitigated secondary immunodeficiency associated with tumor growth, though they did not directly reduce established tumors. Studies in aged mice reported normalization of selected physiological and biochemical parameters, including oxidative stress markers, suggesting potential relevance in age-related immune decline [5].

Across rodent models, thymomodulin consistently demonstrates broad immunostimulatory and immunorestorative activity, affecting myelopoiesis, lymphocyte maturation, antibody production, and innate immunity. Importantly, no significant toxicity has been observed even at relatively high doses in multiple species [4–6]. These controlled studies provide a strong mechanistic foundation for thymic extract safety and efficacy. Nevertheless, limitations include small sample sizes, specific inbred strains, heterogeneous preparations, and diverse dosing regimens, which complicate standardization. Most experiments addressed induced conditions under laboratory settings rather than naturally occurring diseases, emphasizing the need for well-designed translational and field studies to determine whether these benefits extend to real-world veterinary and production contexts.

Companion Animals (Companion Mammals)

In companion animals, particularly cats and to a lesser extent dogs, thymomodulin has been applied as an immunomodulatory adjunct in both experimental and clinical settings, especially for diseases in which immune competence is a critical determinant. Cats are the best-documented companion species, largely due to the clinical and public health relevance of feline sporotrichosis and retroviral immunodeficiency. Sporotrichosis, caused by *Sporothrix* spp., is a severe fungal infection in cats that is zoonotic and transmissible to humans. Forlani and coauthors (2021) [2] conducted a prospective clinical study in cats with disseminated cutaneous sporotrichosis, evaluating thymomodulin as an adjunct to standard antifungal therapy with itraconazole and potassium iodide. Cats receiving oral thymomodulin alongside antifungals exhibited substantially improved outcomes, with survival rates approaching 94%, nearly double that of cats treated with antifungals alone (~53%). Thymomodulin-treated cats also demonstrated faster lesion resolution, earlier clinical remission, and improved body condition compared with controls. These results indicate that thymomodulin enhanced host immune responses against *Sporothrix*, facilitating fungal clearance and tissue healing. From a One Health perspective, more effective control of sporotrichosis in cats may reduce environmental contamination and the risk of zoonotic transmission to humans [2,14].

Beyond fungal disease, thymomodulin has been explored in immunocompromised cats, particularly those infected with feline retroviruses. In FeLV-positive cats, daily oral thymomodulin for several weeks was associated with improvements in hematological parameters, including normalization of leukocyte and platelet counts and increases in hemoglobin levels [7]. Preliminary reports further suggest increases in circulating immunoglobulins (IgG and IgA) and partial recovery of immune competence [2,7]. These effects are consistent with known myelostimulatory and immunorestorative properties of thymomodulin, indicating potential benefits in reducing susceptibility to opportunistic infections and improving quality of life in chronically infected animals. However, most data derive from small observational studies or preliminary reports, with limited information on study design, statistical power, and long-term outcomes.

In dogs, controlled studies are scarce, with most evidence arising from empirical use or indirect observations. Thymomodulin has been employed off-label as an immunostimulant in dogs with recurrent infections, chronic dermatological conditions (e.g., demodicosis or papillomatosis), and as adjunct support in neoplastic or immunosuppressive states. Veterinary references describe its capacity to stimulate lymphocyte maturation and hematopoiesis, paralleling effects observed in other mammals. Indirect studies on thymic function in aging dogs suggest that enhancement of thymic hormones can rejuvenate immune parameters, supporting the biological plausibility of thymomodulin use in this species. Nonetheless, the absence of controlled clinical trials in canine infectious or immune-mediated diseases represents a significant gap [2].

Across companion animals, thymomodulin has been considered a safe adjunct, with minimal adverse effects reported in clinical practice and no significant toxicity documented in studies [13]. Despite encouraging findings in cats, particularly for sporotrichosis, the evidence base remains limited by small sample sizes, lack of multicenter validation, and incomplete immunological characterization, such as absence of detailed lymphocyte subset analyses, cytokine profiling, and long-term outcomes. Evidence in dogs remains largely anecdotal. Collectively, these limitations underscore the need for larger, well-controlled clinical trials to determine the magnitude, reproducibility, and clinical relevance of its immunomodulatory effects across companion animal species and disease contexts.

Figures 2 and 3 summarized the immunomodulatory effects of thymomodulin across different animal species and its broader implications within the One Health framework.

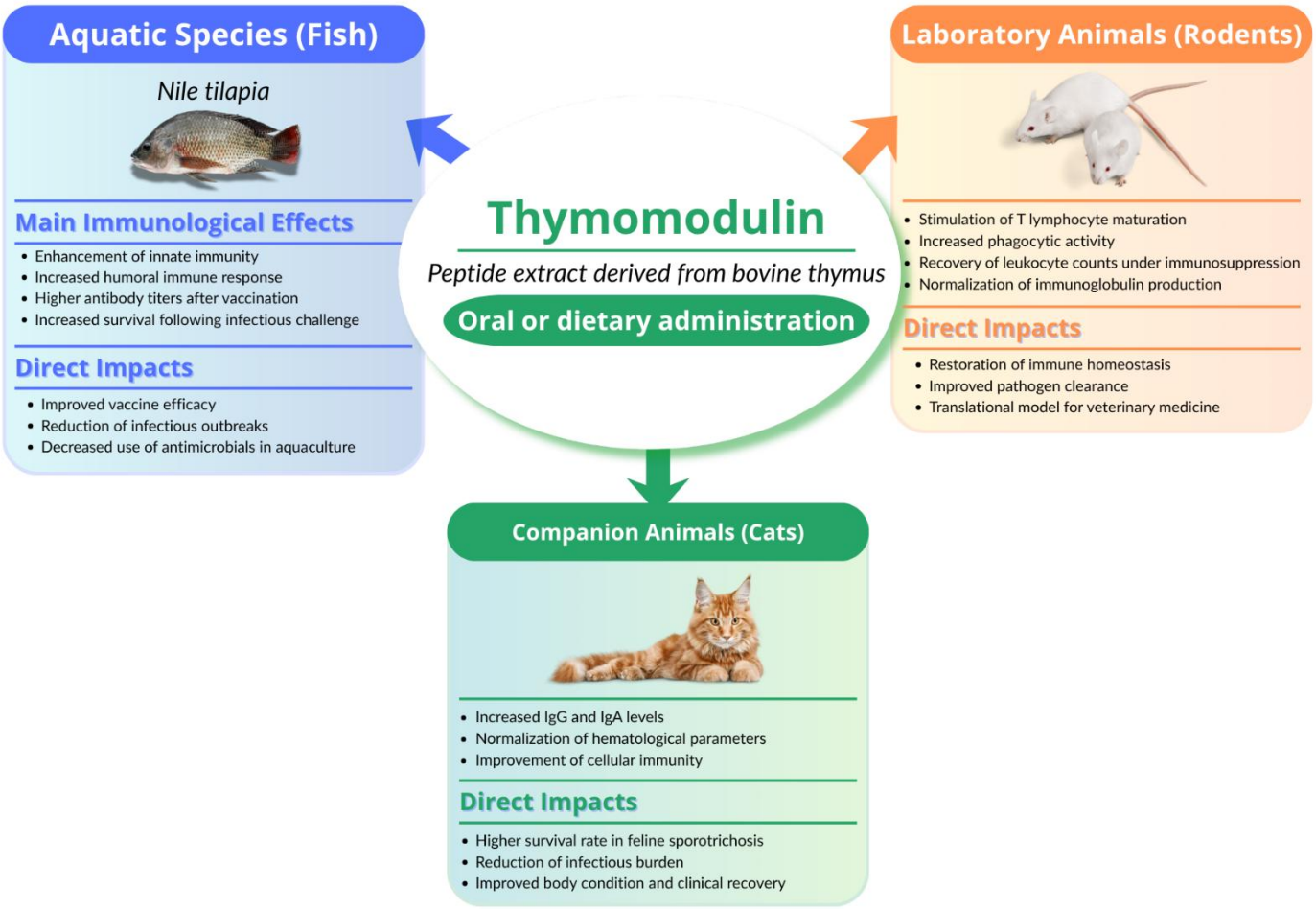

Figure 2. Conceptual representation of thymomodulin-mediated immunomodulatory effects in different animal species

As shown in Figure 2, thymomodulin exerted consistent immunomodulatory effects across aquatic species, laboratory animals, and companion animals. In fish, particularly Nile tilapia, thymomodulin enhanced both innate and humoral immune responses, increased post-vaccination antibody titers, and improved survival following infectious challenge. These immunological effects translated into tangible production-level benefits, including enhanced vaccine efficacy, reduced incidence of infectious outbreaks, and decreased reliance on antimicrobials in aquaculture systems.

In laboratory rodents, thymomodulin promoted T-lymphocyte maturation, increased phagocytic activity, supported leukocyte recovery under immunosuppressive conditions, and normalized immunoglobulin production. These effects contributed to the restoration of immune homeostasis and enhanced pathogen clearance, reinforcing the value of rodents as translational models for investigating its mechanisms of action and therapeutic potential in veterinary contexts.

In companion animals, particularly cats and dogs, thymomodulin administration was associated with increased IgG and IgA levels, normalization of hematological parameters, and improved cellular immunity. Clinically, these immunological improvements corresponded to higher survival rates in infectious diseases such as feline sporotrichosis, reduced infectious burden, and enhanced body condition and overall clinical recovery.

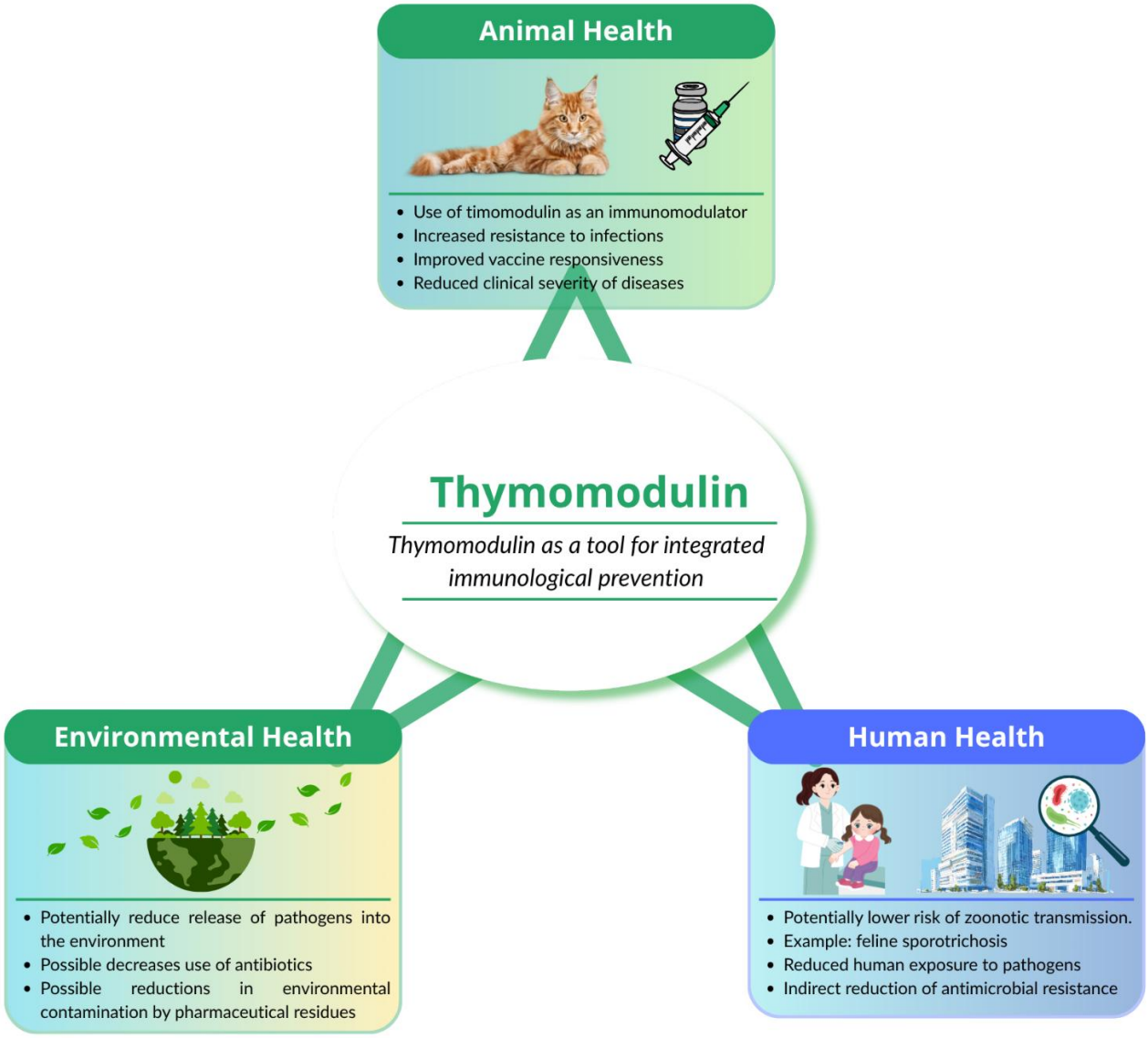

Figure 3. Integration of thymomodulin into the One Health concept.

Figure 3 situates these species-specific effects within a One Health framework. By enhancing animal immune function, thymomodulin may contribute to increased resistance to infections, improved vaccine responsiveness, and reduced clinical disease severity at the animal level. These animal-level outcomes could potentially decrease pathogen circulation and environmental release, and may help reduce antibiotic use in specific contexts, although such effects have not been directly measured in the included studies. Accordingly, the environmental implications, including reduced contamination with pharmaceutical residues, should be interpreted as indirect and hypothesis-generating rather than demonstrated outcomes.

Consequently, thymomodulin could potentially support human health by contributing to reduced zoonotic risk through improved infection control in animals. However, direct evidence of reduced zoonotic transmission, reduced human exposure, or measurable impacts on antimicrobial resistance is not available in the included studies. Collectively, the mapped findings suggest thymomodulin as a promising immunomodulatory agent with potential cross-sector relevance, while highlighting One Health outcomes as research opportunities rather than confirmed effects.

Livestock and Other Species

Beyond laboratory models and companion animals, thymomodulin and analogous calf thymus extracts have been evaluated in a limited number of livestock contexts, although the available evidence remains relatively sparse. This line of research is nevertheless highly relevant, as improvements in immune function in farm animals can yield economic benefits and advance One Health objectives by promoting healthier herds, safer food production, and reduced reliance on antimicrobial drugs.

In poultry, Chandra Naik and coauthors (2005) [8] investigated the use of a calf thymus extract in broiler chickens vaccinated against Newcastle Disease Virus (NDV), a major and economically significant avian pathogen. In this study, day-old chicks were assigned to two groups that both received standard NDV vaccination schedules (a mild “F” strain at one week of age followed by a booster “R2B” strain at eight weeks), while one group additionally received intraperitoneal injections of thymic proteins (1.8 mg) one week before and one week after each vaccination. Fifteen days after vaccination, birds treated with thymus extract exhibited significantly higher antibody titers against NDV, as measured by hemagglutination inhibition assays, increased serum globulin concentrations, and a higher proportion of circulating lymphocytes compared with vaccinated controls. Markers of cell-mediated immunity were also enhanced, including improved responses in mitogen stimulation and delayed-type hypersensitivity tests, indicating a broader activation of cellular immune pathways [8]. Functionally, these findings suggest that thymus extract acted as an immune adjuvant that strengthened vaccine-induced protection, potentially improving flock-level resistance to outbreaks. No adverse effects were reported in treated chickens. However, the study was short-term, focused on immunological endpoints rather than clinical outcomes such as morbidity or mortality after viral challenge, tested only a single dose, and was limited to one breed under experimental conditions, which constrains extrapolation to field settings and to other poultry diseases.

In swine, immunostimulatory supplements administered to pregnant sows were evaluated for their capacity to enhance passive immunity transfer to piglets. In this farm-based study, gestating sows received various supplements, including a calf thymus extract (TFX®), and the immunological quality of colostrum at parturition was assessed. Sows treated with thymus extract produced colostrum with significantly higher IgG concentrations, increased total protein levels, and greater lysozyme activity than untreated controls [5], indicating improved transfer of immune components to neonates. Although piglet clinical outcomes were not directly reported, higher colostral IgG is strongly associated with reduced neonatal mortality and improved early growth, given that piglets are born agammaglobulinemic and depend entirely on colostrum for passive immunity. This application situates thymomodulin as a preventive immunological intervention that may reduce early-life disease burden and, consequently, the need for therapeutic treatments. This approach aligns with One Health principles by supporting healthier livestock populations and potentially decreasing antimicrobial use and zoonotic risk in food production systems [20]. Nonetheless, interpretation of this study is complicated by the concurrent testing of multiple immunostimulants, all of which showed some positive effects, making it difficult to isolate the specific contribution of thymus extract. Moreover, the findings derive from a single herd and management context, limiting generalizability.

Data on other domestic species remain scarce. No contemporary studies between 2000 and 2025 were identified that evaluated thymomodulin in cattle, sheep, or horses for the prevention or treatment of common diseases such as bovine respiratory disease. Historical or anecdotal reports of thymic factors used in calves with diarrhea or immune deficiency exist but largely predate 2000 or lack rigorous documentation. In rabbits, however, thymus extract improved reproductive outcomes in a model of antiphospholipid syndrome, with treated animals showing more live offspring and fewer fetal resorptions, suggesting beneficial modulation of immune-mediated reproductive pathology [5]. Although rabbits are not typical livestock, this finding reinforces the broader potential of thymus extracts in modulating immune dysfunction across species.

Taken together, evidence across livestock and other non-human species remains intriguing but fragmented. Each study addresses different species, diseases, and endpoints, which complicates broad generalization. Nevertheless, a consistent pattern emerges in which thymomodulin and related extracts enhance immune responsiveness in contexts such as vaccination, maternal immunity, and disease prevention. The One Health relevance of these findings is often implicit rather than explicit; for example, improved vaccine efficacy in poultry may reduce viral circulation and improve food safety, while enhanced neonatal immunity in pigs may decrease antibiotic interventions. Significant gaps persist, however, including the lack of robust field trials that assess clinical disease reduction rather than immunological proxies alone, and the absence of optimized formulations and dosing strategies suitable for large-scale farm use, particularly oral formulations that would be more practical than injections.

Across all species categories, thymomodulin and analogous thymus extracts consistently demonstrate immunomodulatory activity affecting both innate and adaptive immune responses. Recurrent patterns include improved vaccine-induced immunity, as shown in fish and poultry by elevated antibody titers and enhanced protection [1,8]; enhanced pathogen control and disease outcomes, evidenced by improved survival in feline sporotrichosis, reduced parasite burdens in rodent infection models, and increased phagocytic activity in vitro; and restoration of immune balance in immunocompromised hosts, such as normalization of immunoglobulin levels in FeLV-infected cats and recovery of immune function in multiple rodent

immunosuppression models [5]. These immunological effects translate into tangible health benefits, including increased survival, faster recovery, or improved prophylactic protection, depending on the context.

Safety has been consistently reported as favorable, with no severe adverse effects observed in animal studies and no significant toxicity reported even at relatively high doses [5]. This safety profile is concordant with long-standing human use of thymomodulin, which is generally well tolerated, with only rare allergic reactions documented [1,2]. Within a One Health framework, these characteristics are particularly relevant, as safe immunomodulatory interventions in animals may reduce pathogen shedding, lower zoonotic transmission risk, and decrease antimicrobial consumption, thereby contributing to the mitigation of antimicrobial resistance at the human–animal–environment interface [13].

Despite these promising signals, important evidence gaps remain. The existing literature is heterogeneous and often preliminary, with limited data in certain populations such as dogs, horses, and wildlife, and few well-designed, randomized, and blinded field trials in livestock. Many studies rely on small sample sizes, short follow-up periods, and surrogate immunological endpoints rather than clinically meaningful outcomes such as disease incidence, survival, or productivity. Furthermore, there is a lack of standardization across thymomodulin preparations, dosing regimens, and routes of administration, which hampers comparability and translational applicability. Addressing these population, context, design, outcome, and intervention gaps will be essential for defining the true role of thymomodulin within preventive and therapeutic strategies in veterinary medicine and for clarifying its potential contribution to One Health goals. The mapping table (Table 1) provided below summarizes the key included studies, their species and contexts, reported outcomes, limitations, and identified evidence gaps, thereby offering a structured overview of current knowledge and priorities for future research.

Table 1. Evidence Mapping Table

Species	Condition or Context	Study Design	Setting	Intervention (*Thymus* Extract type)	Dose and Regimen	Route	Comparator	Immune outcomes reported	Clinical/ Vaccine outcomes	One Health interface	Key limitations (as noted by authors)	Evidence gap tag
Tilapia (Nile fish)	Vaccination against *Streptococcus agalactiae* (bacterial infection)	Factorial controlled trial (dietary supplement + vaccine)	Experimental fish tanks (aquaculture research)	Thymomodulin (calf thymus acid lysate) mixed in feed	0.3% of feed for 30 days pre-vaccination	Oral (in feed)	Vaccinated fish without thymomodulin (and unvaccinated controls)	↑ Specific anti-*Streptococcus* antibody titers post-vaccination; enhanced innate protection indicators (unspecified, presumed phagocyte activity)	↑ Survival after live *S. agalactiae* challenge (improved disease resistance); overall protection better than vaccine-alone group	Indirect: healthier fish -> less antibiotic use in aquaculture (reducing AMR risk)	Single species and pathogen; short-term observation (post-challenge only); done in controlled lab setting (may differ in field ponds)	Population /Context (only tilapia, Strep vaccine context)
Chicken (Layer chicks)	Newcastle Disease vaccination (viral vaccine)	Controlled trial, two groups (with vs. without extract)	Experimental farm setting (research flock)	Calf Thymus Extract (CTE, thymic proteins)	1.8 mg (protein) per bird, i.p. one week before and after each vaccination (two vaccine rounds)	Intra-peritoneal injection	Vaccinated control group (no CTE)	↑ NDV antibody titers (HI titers); ↑ serum globulins; ↑ blood lymphocyte percentage; enhanced cell-mediated immunity (stronger DTH/cell response)	Not directly measured (presumed better protection; outcome: significant immunopotentiation of vaccine)	Indirect: improved livestock vaccine response -> food security, less risk of NDV spread to wild birds	No challenge infection to confirm clinical protection; one breed/strain of chickens; extract dosing via injection not practical for large flocks	Context/ Design (artificial setting, immunological endpoints only)
Cat (domestic short-hair)	Disseminated sporotrichosis (fungal infection), severe cutaneous form	Prospective controlled trial (adjunct therapy vs. standard care)	Veterinary clinical setting (Brazil; pet cats)	Thymomodulin (Leucogen®) adjunct to antifungals	4 mg/kg daily, with standard itraconazole + potassium iodide therapy (8–12 weeks)	Oral (capsules or suspension)	Standard antifungal therapy alone (no thymomodulin)	↑ Immunoglobulins (not measured in this study, but other cat studies show Ig rise) – primary immune outcome not directly reported in this study, focus was clinical	Doubled survival rate (94% vs 53%); faster lesion healing and recovery; improved body condition	Yes – *Sporothrix* is zoonotic; treating cats more effectively lowers human exposure risk	Not randomized (allocation by owner consent); moderate sample (n≈35); all cats from one region/epidemic; no detailed immune profiling	Design (lack RCT rigor; no immune markers)
Cat	FeLV infection (feline leukemia virus, causing immunosuppression)	Uncontrolled pilot study (pre/post comparison)	Veterinary clinic / academic study (Brazil)	Thymomodulin (Leucogen®) as immunostimulant therapy	10 mg per cat, twice weekly for 4 weeks (exact regimen not	Oral (by capsule) or subcutaneous (unclear)	No placebo or control (baseline values as reference)	↑ IgG and IgA levels post-therapy; normalization of WBC counts (improved lymphocyte counts noted)	Not reported in detail; anecdotal reports of improved vitality, fewer secondary infections	Indirect: FeLV is not zoonotic, but stronger immunity may reduce co-infections that can carry zoonotic agents (e.g. toxoplasmosis)	Forthcoming study, limited data; very small sample; no control group or randomization; outcomes mainly laboratory values	Design/Reporting (pilot data, lacks controls)

Cont. Table 1

Mouse (laboratory strain)	Helminth infection – Trichinella spiralis (parasitic nematode)	Repeated experimental infection studies (treated vs untreated infected mice)	Lab research setting (parasitology experiments)	Thymus extract (TFX-Thymomodulin® from calf thymus)	~10–20 mg/kg, injected s.c. or i.p., given post-infection	Subcutaneous / Intraperitoneal	Infected mice without immunomodulator	↑ Inflammatory leukocytes around larval cysts in muscle; ↑ apoptotic lymphocyte percentage in infected tissues (suggesting immune activation); modulated T-cell phenotypes (infection-induced changes enhanced)	↓ Muscle larval burden (fewer T. spiralis larvae survived); faster parasite clearance from tissues	Not direct (lab model of zoonotic parasite – implies potential to reduce transmission if applied in food animals or wildlife)	Animal model only, not a natural host (mice, not pigs/humans who get Trichinella); high experimental parasite doses; different extract preps across studies; translational relevance to field conditions unknown	Context (model-specific, not directly field-applied)
Rat (Lewis strain)	Autoimmune EAE (Experimental Allergic Encephalomyelitis – model of multiple sclerosis)	Experimental therapeutic trial (induced EAE, treated vs placebo)	Laboratory (neurological disease model)	Calf thymus extract (TFX®) or fraction thereof (peptide mix)	10 mg/kg, intramuscular, given as both prophylactic (pre-disease) and therapeutic (during disease) in different arms	Intramuscular injection	EAE induced rats without TFX (saline injections)	↑ Regulatory immune effects inferred: reduced inflammatory markers in CNS, limited demyelination (exact immune assays not given, but improved immunological milieu in CNS)	↓ Clinical severity of paralysis; histological improvement in spinal cord lesions; delayed onset of symptoms	Not direct (rat model for human disease; no immediate zoonotic link)	Specific to MS model in rodents; relevance to veterinary neuro diseases unclear; small n; outcomes partly subjective (clinical scoring)	Context/Population (species-specific model, not generalizable)
Pregnant Sow (pig)	Prophylaxis for neonatal immunity – improve colostrum quality	Field trial (supplements vs none in late gestation)	Farm setting (breeding herd)	Thymus extract (TFX®) as feed supplement during pregnancy	~20 mg per day in feed, last 3–4 weeks of gestation (with vitamins in regimen; from study protocol)	Oral (feed additive)	Pregnant sows with no immunostimulant supplement	↑ Colostrum IgG concentration; ↑ colostral total protein and lysozyme (enhanced innate factors); no negative effect on sow health	Not directly measured in study, but expected: heavier piglets, lower piglet mortality (not reported; authors infer better passive transfer may improve piglet survival)	Yes – stronger passive immunity in livestock -> less neonatal disease, reducing need for antibiotics (impact on AMR and food safety)	Combination of interventions (TFX plus other additives, results not isolated); no follow-up on piglet health; single farm study	Design (confounded intervention; lacking direct piglet outcome data)

In total, this scoping review included a small number of relevant studies (seven sources met the inclusion criteria), reflecting the nascent and fragmented nature of the evidence base for thymomodulin in animals. The included evidence encompassed a range of study types and models: two controlled trials in aquatic and avian species (fish and chickens), one controlled clinical study in companion animals (cats), one uncontrolled pilot study in cats, two laboratory experiments in rodents (mice and rats disease models), and one field-based pilot trial in livestock (sows). No controlled studies in dogs or wildlife were identified, and data for those groups remain limited to anecdotal or grey literature references. The heterogeneity across these studies is considerable, spanning diverse species, health conditions, and outcome measures.

Common characteristics of the included studies were the measurement of immune parameters (such as antibody titers, leukocyte counts, or lymphocyte functions) and, in some cases, clinical or survival outcomes following disease challenge or during therapy. Many studies reported beneficial immunomodulatory effects of thymomodulin or thymus extracts, including enhanced antibody production, restoration of cell counts in immunosuppressed animals, and improved clinical recovery or survival. These outcomes were observed in both prophylactic settings (e.g., vaccine response in fish and poultry, neonatal immunity in piglets) and therapeutic or adjunctive settings (e.g., feline sporotrichosis, FeLV infection, rodent infection models).

Despite these promising findings, the strength of evidence is generally limited. There is substantial heterogeneity in study designs (ranging from small uncontrolled case series to controlled trials), sample sizes (often very small, sometimes under 10 animals per group in rodent studies, or a few dozen in clinical studies), and interventions (different thymus extract preparations, doses, and routes). The outcomes measured also vary widely, from immunological surrogate markers (e.g., antibody levels, cell counts) to clinical endpoints (survival, lesion healing), making direct comparisons and generalizations difficult. Notably, many studies focused on surrogate immune outcomes rather than long-term clinical outcomes like disease incidence, severity, or productivity, which limits the practical conclusions that can be drawn for field applications.

The evidence base also has clear limitations. Several studies lacked rigorous design features such as randomization or blinding, raising the possibility of bias. For instance, the feline sporotrichosis study was controlled but not randomized, and the FeLV pilot lacked a control group entirely. Small sample sizes and single-location studies prevail, meaning results may not be statistically robust or broadly generalizable. Additionally, there is a lack of standardization across thymomodulin preparations: different products (or crude thymus extracts) with varying peptide composition were used, and dosing regimens ranged widely. This lack of standardization could influence efficacy and makes it challenging to reproduce or compare results across studies. Lack of randomization and blinding increases the risk of selection, performance, and detection bias, potentially confounding observed outcomes, particularly when clinical or semi-quantitative immunological endpoints are used. Small sample sizes further limit statistical robustness and may inflate apparent effect sizes. In uncontrolled or pilot studies, improvements cannot be definitively attributed to thymomodulin due to possible spontaneous recovery or concurrent interventions. Therefore, although the findings are suggestive, they should be interpreted cautiously and considered preliminary rather than confirmatory.

Across the evidence included, few studies provided detailed mechanistic insights. Most did not include advanced immunological analyses such as cytokine profiling or immune cell subset characterization, which constrains our understanding of how thymomodulin exerts its effects and in which contexts it is most effective. Long-term safety and efficacy data in animals are scarce; while chronic human use of thymomodulin has suggested a favorable safety profile [26], similar long-term studies in animals have not been performed, leaving potential gaps in safety or resistance outcomes unaddressed.

It should also be noted that some of the evidence necessarily relies on older references or grey literature, due to the limited amount of recent peer-reviewed research on certain aspects. For example, foundational studies from the 1980s-1990s and early 2000s [3,4,6,26] are cited to provide historical context and basic mechanistic understanding of thymomodulin, as more up-to-date data are not available for those particular mechanisms. Likewise, in areas such as canine use of thymomodulin where no formal studies were found, we have referenced veterinary technical resources (e.g., a product monograph [13]) to acknowledge what is known in practice. The inclusion of these older or non-peer-reviewed sources is justified by their historical and technical value, but it underscores the need for contemporary research to validate and expand upon those findings.

Overall, the nature and strength of evidence for thymomodulin in animals can be characterized as emerging and moderate-to-low. Table 2 provides a concise summary of the evidence by species category, highlighting the type of studies available and a qualitative assessment of evidence strength in each case. This summary underscores that, while biologically plausible benefits of thymomodulin are documented across different animal species, the evidence in each category is limited in volume and quality, warranting cautious interpretation. Key limitations such as heterogeneity of methods, small scales, and reliance on surrogate

outcomes suggest that further research is required to confirm these early findings and translate them into solid recommendations.

Table 2. Summary of evidence by species category, study type, and evidence level.

Animal category	Predominant study types	Evidence level
Aquaculture (fish)	One controlled experimental trial (vaccine-challenge in tilapia) [1]	**Moderate:** Proof-of-concept from a single study (significant effects but limited scope).
Poultry (chickens)	One small controlled vaccine trial in research flock [8]	**Low-moderate:** One study showing immune benefits; needs replication in field conditions.
Companion cats	One controlled clinical study (sporotrichosis) [2]; one pilot observational study (FeLV) [7]	**Moderate:** Encouraging results in small trials, but evidence base is limited in size and breadth.
Companion dogs	Anecdotal and off-label use reported; no controlled studies (only veterinary monograph info) [13]	**Low:** No direct research evidence; current knowledge based on extrapolation and expert opinion.
Laboratory rodents	Multiple experimental studies (infection, immunosuppression models) [5,19]	**Moderate:** Consistent immunological effects shown in lab settings; strong mechanistic support, but not directly clinical.
Livestock (swine)	One pilot field trial in sows (colostrum immunity) [20]	**Low:** Limited data with confounded intervention; evidence of benefit tentative and not yet corroborated.

This summary highlights that fish, cats, and rodent models have moderate evidence mainly because of demonstrable effects in controlled settings, whereas dogs, poultry, and livestock applications currently rest on low evidence (one or no studies, or purely observational/technical information). No category has what would be considered high-level evidence, reflecting the early stage of research on thymomodulin in the animal health domain.

DISCUSSION

Thymomodulin exhibits consistent immunomodulatory effects across a wide range of species, including fish, laboratory rodents, companion animals, poultry, and swine, indicating the presence of conserved underlying mechanisms alongside species-specific nuances. A central pattern observed is that thymomodulin functions primarily as an immune normalizer or enhancer, with more pronounced effects in individuals with compromised or immature immunity (due to stress, infection, or young age). Mechanistically, thymomodulin appears to exert a pro-thymic function by supplementing or mimicking endogenous thymic activity: it promotes T-cell maturation and cytokine production, and secondarily stimulates B cells and innate effector cells [6]. This mechanism aligns with the increased antibody production, enhanced phagocytic activity, and restoration of leukocyte counts documented in immune-depleted subjects. Such effects were observed across evolutionarily distant taxa. In fish, which lack bone marrow and lymph nodes, thymomodulin supplementation increased antibody responses and post-infection survival [1], suggesting activation of thymus- and spleen-dependent lymphopoiesis. In mammals, thymomodulin directly stimulated both lymphopoiesis and myelopoiesis, evidenced by neutrophil and T-cell recovery in mice [2] and increased immunoglobulin levels in cats [7]. This is consistent with the hypothesis that thymomodulin either induces the release of endogenous thymic factors or provides exogenous thymic peptides that help correct immune deficiencies.

Despite these shared mechanisms, responses vary across species and contexts. Effective dose, timing, and route of administration differ oral administration is effective in humans and cats [13], and as a feed additive in fish, whereas several rodent studies employed injectable formulations. Fish display limited adaptive immune memory relative to mammals, which makes the marked antibody enhancement observed in thymomodulin-fed tilapia particularly notable and suggestive of adjuvant-like properties [1]. In mammals, thymomodulin may exert subtler regulatory effects on cytokine profiles and immune balance – for example, other research has noted increased IL-2 production in aged mice or reduced IL-6 in autoimmune models – although such parameters were rarely assessed systematically in the studies we reviewed. Importantly, no reviewed study reported pathological immune overstimulation or induction of autoimmunity; this supports the interpretation that thymomodulin promotes a balanced restoration of immune function rather than indiscriminate immune activation. The immunoregulatory profile of thymomodulin appears context-dependent and will require deeper immunophenotyping in future studies to fully elucidate.

From a One Health perspective, these immunological effects may offer broader benefits for human, animal, and environmental health, although such impacts remain inferential. To substantiate these potential advantages, future studies should incorporate explicit One Health outcome measures. Controlled field trials

in livestock and aquaculture could quantify antimicrobial consumption before and after thymomodulin implementation, alongside microbiological surveillance of pathogen prevalence and resistance profiles. In companion animals, longitudinal studies could assess pathogen shedding dynamics to evaluate effects on environmental contamination and zoonotic transmission risk. Environmental endpoints, such as antimicrobial residue monitoring in soil or water, would further clarify ecological impact. Integrating epidemiological modeling with immunological and microbiological data will be essential to determine whether thymomodulin can meaningfully influence antimicrobial resistance patterns, zoonotic transmission, and environmental pathogen burden [2,11,14].

The translational trajectory of thymomodulin reflects both its promise and its current limitations. Early patents and experimental pharmacology in the late 20th century established its immunostimulatory and anti-leukopenic effects in animal models, providing a mechanistic basis for therapeutic development (e.g., US patents from 1972 and 1983 documented thymus extract therapies [21,22]). Subsequent patent filings into the 1990s and 2000s focused on pharmaceutical stabilization and synergistic formulations for broad immunomodulatory use across species [23–25]. This progression supported the development of standardized commercial thymomodulin products for veterinary use (e.g., to support immune function in dogs and cats with leukopenia). However, translation into widespread practice remains incomplete. Most of the evidence for thymomodulin efficacy remains preclinical or limited to small-scale clinical and field studies, and thymomodulin has not yet been incorporated into mainstream veterinary treatment guidelines. It therefore currently occupies an intermediate translational stage since it is a biologically validated and pharmaceutically developed intervention, but it lacks large-scale clinical consolidation and acceptance.

To further clarify the developmental status of thymomodulin, we can consider its translational positioning in terms of Technology Readiness Levels (TRL), a framework that describes the maturity of a technology or intervention from basic research to full application. While TRL terminology originates from engineering and defense sectors, it can be applied in a veterinary biomedical context to gauge how close thymomodulin is to routine use. The immunobiological effects of thymomodulin have been demonstrated in controlled laboratory studies and experimental models (e.g., rodent infection models, in vitro assays) indicating successful proof-of-concept. In the TRL scale, the extensive animal model data and mechanistic insights correspond to approximately TRL 2-3, where principles have been observed and experimentally confirmed in the lab. The consistency of results across different research groups and conditions gives confidence in the underlying concept at this stage.

Thymomodulin has also been tested in limited field or clinical contexts, such as the feline sporotrichosis study and the tilapia and poultry vaccine studies, where it showed efficacy in the target species under real or semi-real conditions. These examples represent TRL 4-5, wherein the intervention is validated in a relevant environment (pilot-scale studies or small clinical trials). For instance, the cat clinical study and pig field trial demonstrate initial translational application in veterinary practice, albeit on a limited scale. At present, thymomodulin has not reached higher TRLs in the veterinary field. TRL 6-7 would entail larger-scale trials, multi-center studies, or routine demonstration in an operational environment (e.g., widespread use in farms or clinics with proven outcomes). Such data are currently lacking. Thymomodulin is not yet an established component of standard veterinary protocols; evidence of broad efficacy and practical feasibility (cost, delivery, regulatory approval) is needed to move into these later stages. No large field trials or regulatory-driven studies (equivalent to pivotal Phase III trials in human medicine) have been completed.

In summary, based on the data reviewed in this manuscript, translational readiness of thymomodulin in veterinary medicine can be described as preliminary to intermediate. In laboratory and experimental contexts it is well supported, and in certain clinical scenarios it has shown promise. However, substantial work remains to progress thymomodulin to a high readiness level where it could be considered a proven, widely adopted technology for improving animal and One Health outcomes. Recognizing these TRL levels helps to frame expectations. Thymomodulin is not yet “market-ready” as a broadly endorsed intervention, but it has cleared initial scientific hurdles and warrants further development to bridge the gap between research and routine practice.

This scoping review mapped evidence from 2000 to 2025 and identified consistent immunopotentiation across species and contexts, including vaccine adjuvanticity, enhanced infection recovery, and immune restoration in immunosuppressed states. These effects often translated into improved survival, faster recovery, and greater disease resistance in the studied scenarios, particularly in cats, where clinical studies demonstrated substantial benefits in severe infections (sporotrichosis). In livestock and aquaculture, prophylactic immune modulation using thymomodulin remains less developed but shows promise as a non-antibiotic strategy for disease prevention [14]. Laboratory models support these applications mechanistically but also reveal that factors like dosing, formulation, and timing strongly influence outcomes.

Nevertheless, the evidence base shows substantial heterogeneity. Studies differ widely in design, scale, species, thymus extract formulations, and outcome measures, which limits direct comparison and generalization of findings. Many studies involved very small cohorts of animals, lacked rigorous design elements (randomization or blinding), and focused on surrogate immune markers rather than clinically meaningful endpoints. Standardization of thymomodulin preparations remains limited, and variability in peptide composition, extraction methods, and storage conditions may result in biologically distinct products being evaluated under the same designation, compromising cross-study comparability. Future research should prioritize harmonized manufacturing and characterization protocols, including defined peptide fingerprints using validated analytical methods (e.g., HPLC or mass spectrometry) and the establishment of reference standards specifying acceptable ranges of composition, purity, and biological activity. Batch-to-batch quality control supported by functional in vitro bioassays would help ensure biological equivalence. In parallel, dosing regimens should be standardized based on pharmacokinetic and pharmacodynamic studies in target species. The adoption of consensus reporting guidelines detailing formulation characteristics and dosing protocols would further improve transparency, reproducibility, and enable future meta-analyses [26].

To reduce heterogeneity and strengthen the evidence base, future studies should prioritize adequately powered, multicenter randomized controlled trials with harmonized protocols, clearly defined inclusion criteria, and standardized, clinically meaningful endpoints (e.g., infection rates, survival, antimicrobial consumption, and validated immunological markers). The development of consensus reporting guidelines—including detailed characterization of extract composition, peptide profile, dosage, route, and treatment duration—would enhance transparency and reproducibility. Standardized manufacturing processes and validated bioassays are also essential to ensure batch-to-batch consistency. Finally, integrating advanced immunophenotyping techniques with longitudinal follow-up designs would provide deeper mechanistic insight and more robust evaluation of long-term safety and durability of immunological effects.

Despite these limitations, the collective evidence supports thymomodulin as a versatile immunotherapeutic agent that enhances immune competence rather than directly targeting pathogens. Its optimal role may lie in complementing vaccines and antimicrobial therapy, as observed in feline sporotrichosis (improved treatment outcomes alongside antifungals) and in vaccination studies in fish and poultry (heightened vaccine responses). This complementary function aligns with One Health strategies that emphasize prevention, immune resilience, and reduced dependence on antimicrobials. Future research should prioritize well-controlled veterinary trials and integrated One Health outcome evaluations (such as measuring impacts on antimicrobial usage and pathogen shedding [14]), as well as dose-response optimization, deeper mechanistic immunology studies, and standardization of formulations. These steps are needed to determine whether thymomodulin can transition from an experimental immunotherapy to an established component of preventive veterinary and public health practice.

CONCLUSION

Thymomodulin has emerged as a relevant immunomodulatory agent in veterinary and comparative immunology, with evidence of activity across multiple species and disease contexts. This review indicates that thymomodulin enhances both innate and adaptive immunity, translating into meaningful health benefits in research settings, including improved vaccine responses and survival in fish, restoration of immune competence in laboratory models, and higher survival and faster recovery in companion animals with severe infections. These effects support the concept that thymomodulin functions primarily as an immune normalizer, reinforcing host defenses when they are compromised rather than acting as a nonspecific stimulant. Such properties align closely with One Health principles, as strengthening animal immunity could contribute to safer food production, potentially reduced zoonotic transmission, and decreased reliance on antimicrobials through prevention rather than treatment.

Beyond its direct biological effects, thymomodulin represents a translational bridge between basic immunology and applied veterinary and public health practice. Its origin from thymic peptides situates it within a conserved immune pathway, which may explain its cross-species efficacy from fish to mammals. The consistent safety profile reported across studies further supports its suitability for preventive and adjunctive use. However, translation into routine practice remains incomplete. Existing studies are heterogeneous in design, scale, and outcome measures. Standardized dosing regimens, formulations, and field-based evaluations, particularly in livestock and at the population level, are largely lacking. This limits the ability to define evidence-based guidelines and to assess impacts on key One Health indicators such as antimicrobial usage, pathogen shedding, and zoonotic risk in real-world scenarios.

In conclusion, thymomodulin and comparable calf thymus extracts are promising immunomodulators in veterinary medicine, fitting into a preventive, immunocentric approach to animal health that resonates with

One Health objectives. Although current evidence is fragmented and largely exploratory, with some information drawn from older foundational studies or grey sources due to a lack of recent data, it provides a strong biological rationale for further investigation. Well-designed comparative trials and field studies, coupled with mechanistic research and improved formulation development, are now required to update and consolidate thymomodulin role. Future research should prioritize long-term safety evaluations across species and production systems, including chronic administration studies and pharmacovigilance strategies to detect rare or delayed adverse effects. Comprehensive pharmacokinetic and pharmacodynamic characterization in target species will be essential to optimize dosing and assess potential interactions with vaccines or antimicrobials. Translational research integrating immunology, field epidemiology, and health economics is also needed to determine feasibility, cost-effectiveness, and scalability in routine veterinary practice. Large-scale, multicenter field trials incorporating antimicrobial stewardship metrics, pathogen surveillance, and environmental monitoring will be critical to demonstrate real-world impact and define whether thymomodulin can evolve from an adjunct experimental therapy to a standardized component of integrated veterinary and public health strategies.

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Use of Generative Artificial Intelligence

The authors declare that large language models and other generative artificial intelligence (AI) or AI-assisted technologies cannot be credited as authors and have not been listed as authors of this paper.

The authors declare that generative artificial intelligence (AI) or AI-assisted tools were used under full human supervision. The tool(s) and version(s) used, and their purpose, are described here: ChatGPT. No confidential or sensitive data were uploaded to such tool(s), and all AI-assisted content was checked, corrected and approved by the authors, who take full responsibility for the integrity and originality of the manuscript.

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