Research Article

Shifting Paradigms in Tilmicosin Research in Veterinary Medicine: A Bibliometric Perspective on Emerging Risks and Innovations

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Abstract | Tilmicosin, a semi-synthetic macrolide, remains important for managing respiratory diseases in livestock, yet a comprehensive quantitative synthesis of its research landscape is lacking. This study aims to map global tilmicosin research through bibliometric analysis, highlighting publication trends, key themes, influential contributors, and directions for future investigation. A comprehensive bibliometric analysis was conducted using Scopus database. Bibliographic data were analyzed using VOSviewer and Bibliometrix R package to generate network visualizations, thematic maps, and collaboration patterns. Key metrics included publication growth, authorship patterns, institutional contributions, international collaboration, thematic evolution, trend topics and keyword co-occurrence. The analysis retrieved 315 articles spanning 154 journals with an annual growth rate of 4.96%. Chinese institutions dominated with 88 manuscripts (27.9%), followed by the USA (21 manuscripts, 6.7%). Research themes evolved from early pharmacokinetics and efficacy studies toward cardiotoxicity, oxidative stress, and antimicrobial resistance. International collaboration remained limited (12.38%). Early research focused primarily on pharmacokinetics and therapeutic efficacy, while recent studies focused on cardiotoxicity, oxidative stress, antimicrobial resistance, residue detection, and advanced drug-delivery systems such as nanostructured lipid carriers. Thematic mapping revealed pharmacokinetics and bovine respiratory disease as core motor themes, with cardiotoxicity and resistance-related topics emerging prominently over the past decade. Tilmicosin research has evolved from livestock applications to the interface of veterinary medicine, public health, and environmental science. Future research should focus on toxicity studies, overcoming antimicrobial resistance, novel delivery systems, and underexplored animal species to support sustainable veterinary antimicrobial use.

Keywords: Tilmicosin; bibliometric analysis; macrolide antibiotics; veterinary pharmacology; antimicrobial resistance; bovine respiratory disease; cardiotoxicity

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INTRODUCTION

Tilmicosin is a 16-membered macrolide antibiotic, which showed advantages over 14- and 15-erythromycin-based macrolides (Arsic *et al*., 2018). It was first introduced into veterinary medicine in the late 1980s and has since played a substantial role in the prevention and treatment of infectious diseases in food-producing animals (Norcia *et*

al., 1999; Tyshkivska *et al*., 2021). Its mechanism of action is similar to general macrolides antibiotics and involves inhibition of bacterial protein synthesis through binding to the 50S ribosomal subunit (Papich, 2016). Tilmicosin is effective on major causes of respiratory diseases in bovines and swines, including Mycoplasma spp., *Pasteurella multocida*, *Mannheimia haemolytica* (Papich, 2021). The drug's unique pharmacokinetic profile, characterized by extensive tissue distribution, preferential accumulation in lung tissues, and slow elimination, has supported its clinical applications (Chen *et al*., 2023).

Classical investigations on tilmicosin focused on therapeutic value (Paradis *et al*., 2004), and pharmacokinetics (Clark *et al*., 2008; Xiong *et al*., 2019; Zhang *et al*., 2023). In recent years, tilmicosin has been examined for resistance development (Huang *et al*., 2020) and its mechanisms (Chen *et al*.,2024). Recent evidence suggests that macrolide exposure, including tilmicosin, may influence microbial community structure and facilitate the dissemination of resistance (Burr *et al*., 2022; Chen *et al*., 2024). One of the considerable focuses on tilmicosin is its toxicity, especially its cardiotoxicity and neurotoxicity (Forrester, 2005; Main *et al*., 1996).

Despite a growing body of research on tilmicosin, no comprehensive quantitative synthesis of its research output and thematic evolution exists. Bibliometric analysis is a technique used to quantify and assess the research themes and research evaluation in a certain research field including antibiotics (Naji *et al*., 2025a, b). This study aims to provide a global overview of tilmicosin research, identify dominant and emerging themes, highlight influential contributors, and identify future research directions to support responsible antimicrobial use and informed decision-making in veterinary medicine.

MATERIALS AND METHODS

Study Design

A comprehensive bibliometric analysis was conducted to evaluate global research trends, authorship, institutional contributions, and thematic development in tilmicosin research.

Data Source and Search Strategy

The Scopus database was used as the sole source for retrieving peer-reviewed articles on tilmicosin. The search query included: (TITLE(Tilmicosin) AND (LIMIT-TO (LANGUAGE,"English")) AND (LIMIT-TO (DOCTYPE,"ar"))). Only articles published in English were included. Only journal articles were included in the final analysis. The search was conducted from inception to August 2025.

Inclusion and Exclusion Criteria

Articles were included if they primarily investigated tilmicosin. Excluded were non-English publications and any form of publications other than research articles.

Data Extraction

Bibliographic information was extracted for each publication, including title, authors, affiliations, journal, year of publication, keywords, total citations, and corresponding author country. Citation metrics included total citations (TC), citations per year (TC/year), and normalized citations (NC). Co-authorship, institutional affiliations, and international collaboration data were also recorded.

Bibliometric Analysis

Descriptive statistics summarized publication output, author productivity, institutional contributions, country participation, and citation impact. Annual scientific production and journal distribution were analyzed to identify annual trends. Authorship patterns, including single- versus multi-author publications and fractionalized contributions, were assessed. Institutional analysis focused on the most productive organizations. International collaborations were evaluated through co-authorship across countries.

Keyword and Thematic Analysis

Author-assigned keywords and Keywords Plus were analyzed to identify core, emerging, and niche research themes. Co-occurrence networks explored relationships among topics and their evolution over time. Thematic mapping classified topics by centrality (relevance) and density (development), enabling the identification of basic, motor, niche, and emerging/declining themes.

Software

Bibliometric mapping and visualization were conducted using VOSviewer (version 1.6.20) (van Eck and Waltman, 2010) and the Bibliometrix R package with the Biblioshiny interface (Darvish, 2020), enabling the creation of interactive and easily interpretable network diagrams.

RESULTS

The tilmicosin literature database comprises 315 peer-reviewed articles published across 154 distinct sources spanning 1988–August 2025. The dataset involved 1222 authors contributing an average of 5.67 co-authors per document, with 11 single-authored publications and 12.38% international co-authorships. Documents accumulated 2576 Keywords Plus, 583 author`s keywords and citing 8325 references. Average document age was 15.1 years with annual growth rate of 4.96%, yielding

17.54 mean citations per document (Table 1).

Table 1: Description of the included studies in tilmicosin research

Description	Results
Timespan	1988:2025
Sources (Journals, Books, etc)	154
Documents	315
Annual Growth Rate %	4.96
Document Average Age	15.1
Average citations per doc	17.54
References	8325
Keywords Plus (ID)	2576
Author's Keywords (DE)	583
Authors	1222

Annual scientific production and leading journals

After sporadic publications in the late 1980s and early 1990s, research activity increased during 1993–2000, with annual outputs ranging from 5 to 13 articles. Publication productivity fluctuated between 2001 and 2018, before a marked rise from 2019 onward. Annual outputs reached 16–17 articles in 2019–2020, peaked at 22 articles in 2024, and remained active in 2025 with six publications recorded to date (Figure 1).

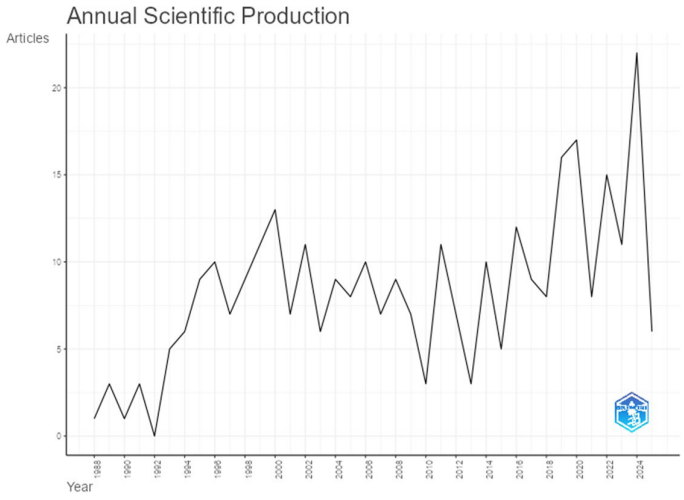

Figure 1: Annual scientific production of tilmicosin research.

Scholarly output was concentrated in a limited number of journals, led by the Journal of Veterinary Pharmacology and Therapeutics (27 articles), followed by the American Journal of Veterinary Research (13 articles). Additional key contributions included the Journal of AOAC International (10 articles), Canadian Veterinary Journal (9 articles), Veterinary Record (7 articles), and Veterinary Therapeutics (7 articles) (Figure 2).

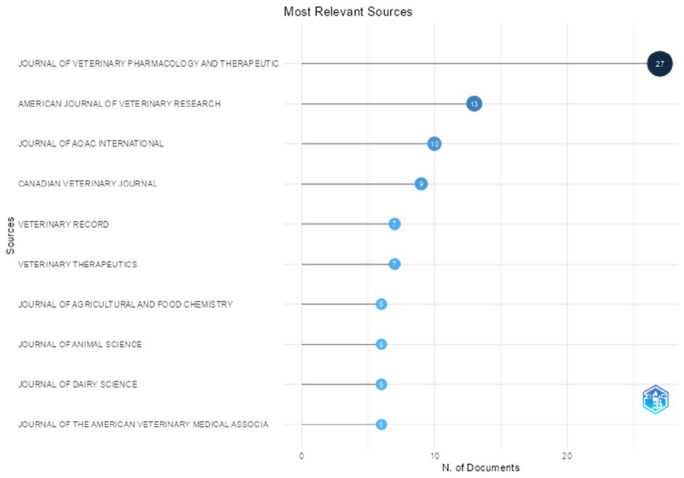

Figure 2: Most relevant resources of tilmicosin research.

Principal authorship contributions and individual research output

Wang Y was the most prolific author with 14 publications, followed by Shryock TR (12 articles), Li X (11 articles), and Wang X (10 articles). Other details can be found in Figure 3.

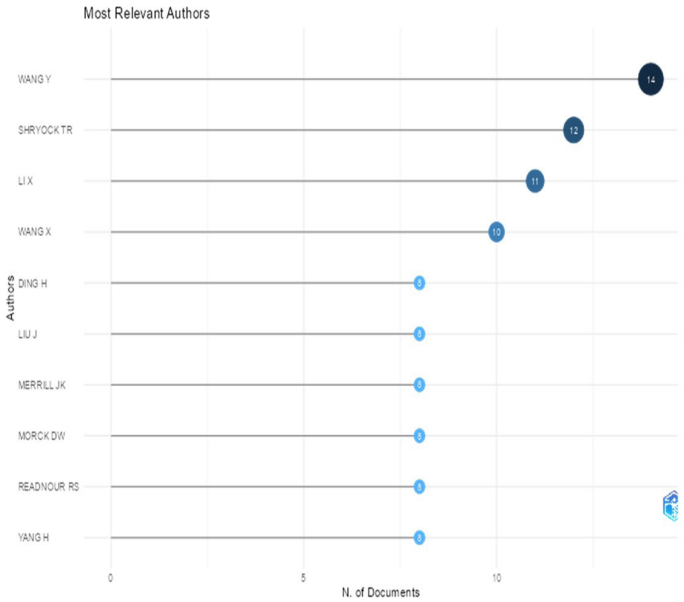

Figure 3: Most relevant authors of tilmicosin research.

Institutionally, output was dominated by Chinese agricultural universities, led by Huazhong Agricultural University (88 articles), South China Agricultural University (74), China Agricultural University (58), Foshan University (48), and Nanjing Agricultural University (43). Secondary contributors included Zagazig University (Egypt; 20 articles), Yangzhou University (China; 19 articles), Benha University (Egypt; 18 articles), Selcuk University (Turkey; 18 articles) and Elanco Animal Health (16 articles) (Figure 4).

Figure 4: Most relevant affiliations of tilmicosin research.

Country contributions and international research collaborations

China-based corresponding authors led with 88 articles, predominantly single-country (88), followed by the United States (21), Canada (18), and Egypt (16). Turkey contributed 13 manuscripts, all single-country (Figure 5).

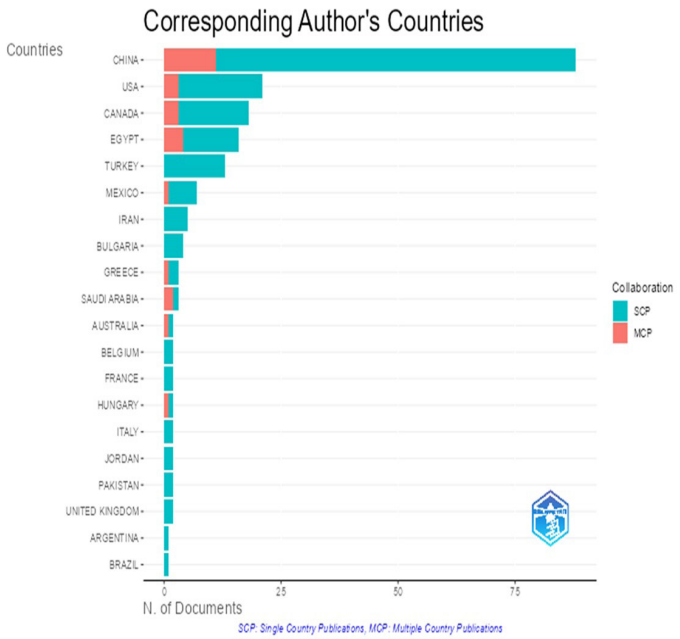

Figure 5: Corresponding authors countries of tilmicosin research.

Institutional affiliation analysis further underscored China's dominance, accounting for 715 affiliations (68.0%), followed by the United States (320), Canada (186), Egypt (91), and Turkey (79) (Figure 6).

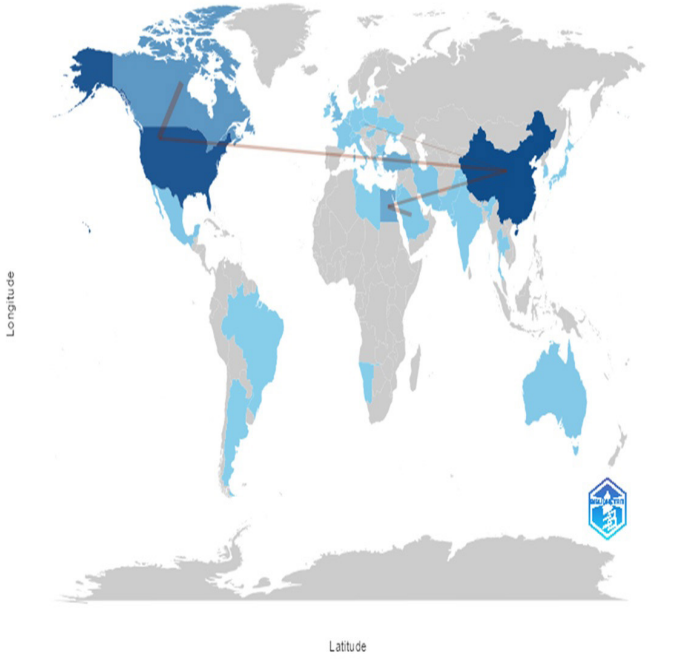

Figure 6: International research production and collaborations of tilmicosin research.

Bilateral international collaborations were evident but limited in scope, led by USA–Canada partnerships with 8 jointly authored articles, representing the most active cross-national linkage. Egypt–Saudi Arabia collaborations followed with 4 publications. China engaged in multiple bilateral partnerships, producing 3 articles each with the USA and Egypt, and 2 articles with the Czech Republic (Figure 6).

The leading tilmicosin studies span cardiotoxicity, enhanced antimicrobial delivery, analytical detection, and pharmacokinetics. Ibrahim *et al.* (2015, 85 citations) showed that tilmicosin causes dose-related cardiotoxicity in mice and that Spirulina supplementation attenuates oxidative cardiac damage (Ibrahim and Abdel-Daim, 2015). Wang *et al.* (2012, 82 citations) demonstrated that tilmicosin-loaded solid lipid nanoparticles significantly enhanced antibacterial activity against Staphylococcus aureus (Wang *et al.*, 2012). Li *et al.* (2019, 79 citations) developed lateral flow immunochromatographic assays for rapid on-site detection of tilmicosin residues in milk and pork for improving field surveillance (Li *et al.*, 2019). Morck *et al.* (1993, 74 citations) established key evidence on the preventive effectiveness of tilmicosin against bovine respiratory disease (Morck *et al.*, 1993). Modric S *et al.* (1998, 69 citations) further characterized drug pharmacokinetics and pharmacodynamics in production animals (Modric *et al.*, 1998). Cheng *et al.* (2017, 68 citations) investigated tilmicosin removal from water (Cheng *et al.*, 2017). Galyean *et al.* (1995, 67 citations) evaluated tilmicosin's effects on animal performance (Galyean *et al.*, 1995), and Debono M *et al.* (1989, 67 citations) reported early antibacterial properties of the compound (Debono *et al.*, 1989) (Table 2).

Table 2: The most highly-cited tilmicosin research. Total Citations (TC) represents the cumulative number of citations received by the article from the time of its publication up to the date of data extraction. Normalized Total Citations (Normalized TC): Normalized TC adjusts the raw citation count by accounting for the publication year and is calculated by dividing an article's actual citation count by the average number of citations received by all articles published in the same year.

Paper	DOI	Total citations	TC per year	Normalized TC
IBRAHIM AE, 2015, CELL J	https://doi.org/10.22074/cellj.2015.520	85	7.727272727	3.014184397
WANG XF, 2012, VET J	https://doi.org/10.1016/j.tvjl.2010.11.019	82	5.857142857	2.28685259
LI X, 2019, SENS ACTUATORS, B CHEM	https://doi.org/10.1016/j.snb.2019.127059	79	11.28571429	3.208121827
MORCK DW, 1993, J AM VET MED ASSOC		74	2.242424242	2.936507937
MODRIC S, 1998, J VET PHARMACOL THER	https://doi.org/10.1046/j.1365-2885.1998.00177.x	69	2.464285714	2.23381295
CHENG J, 2017, J HAZARD MATER	https://doi.org/10.1016/j.jhazmat.2016.11.006	68	7.555555556	2.344827586
GALYEAN ML, 1995, J ANIM SCI	https://doi.org/10.2527/1995.7351219x	67	2.161290323	3.241935484
DEBONO M, 1989, J ANTIBIOT	https://doi.org/10.7164/antibiotics.42.1253	67	1.810810811	2.01

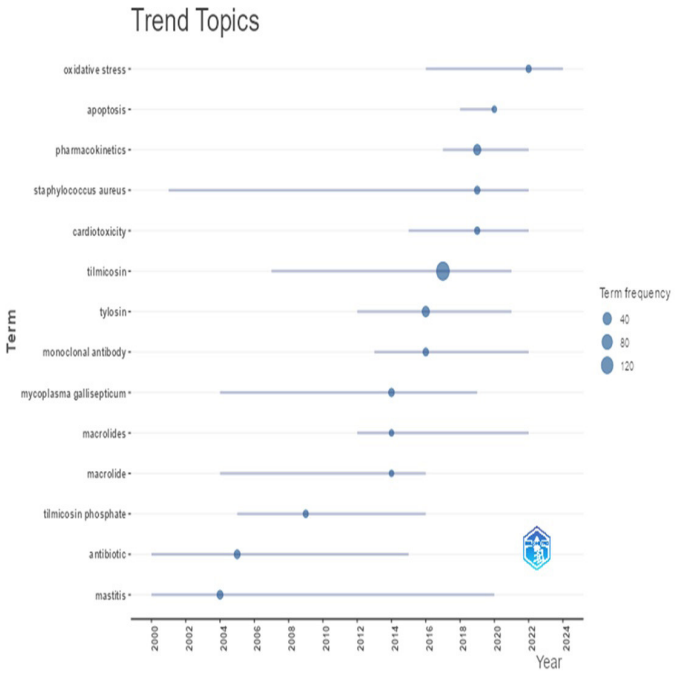

Figure 7: Trend topics of tilmicosin research.

Trend topics

Emerging themes included topics as pharmacokinetics, apoptosis and oxidative stress. Pharmacokinetics was the most frequent among them (22 publications), with output concentrated between 2017 and 2022 (median 2019). Topics such as Staphylococcus aureus (7 publications), cardiotoxicity (6), apoptosis (5), and oxidative stress (6) were largely confined to the last decade, with median publication years clustering around 2019–2022. In contrast, earlier keywords (e.g., mastitis, antibiotic, macrolide and *Mycoplasma gallisepticum*) exhibited broader spans from the early 2000s to 2020 (Figure 7).

Relationship among countries, institutions, sources, and research topics

China dominates the country panel and connects strongly with Huazhong, South China, China Agricultural, Foshan, and Nanjing Agricultural universities, which appear as the most productive organizations. These institutions are mainly linked with journals such as Journal of Veterinary Pharmacology and Therapeutics, Food Chemistry, Poultry Science and Journal of Dairy Science. On the keyword pane, tilmicosin is the primary term, followed by pharmacokinetics, tylosin, mastitis, ELISA, antibiotic, *Mycoplasma gallisepticum*, monoclonal antibody and *Staphylococcus aureus* (Figure 8).

Core, niche, and emerging themes

The thematic map positions clusters by centrality (relevance) and density (development). In the lower-right quadrant, basic themes include tilmicosin phosphate, bovine respiratory disease, mastitis, *Staphylococcus aureus*, cardiotoxicity and creatine kinase. In the upper-right quadrant, motor themes comprise tilmicosin, pharmacokinetic, *Mycoplasma gallisepticum*, antibiotics, representing well-developed, highly connected topics. Niche themes in the upper-left quadrant include metaphylaxis, nanostructured lipid carrier, tylosin and monoclonal antibody while emerging or declining themes include macrolide, infection model and apoptosis (Figure 9).

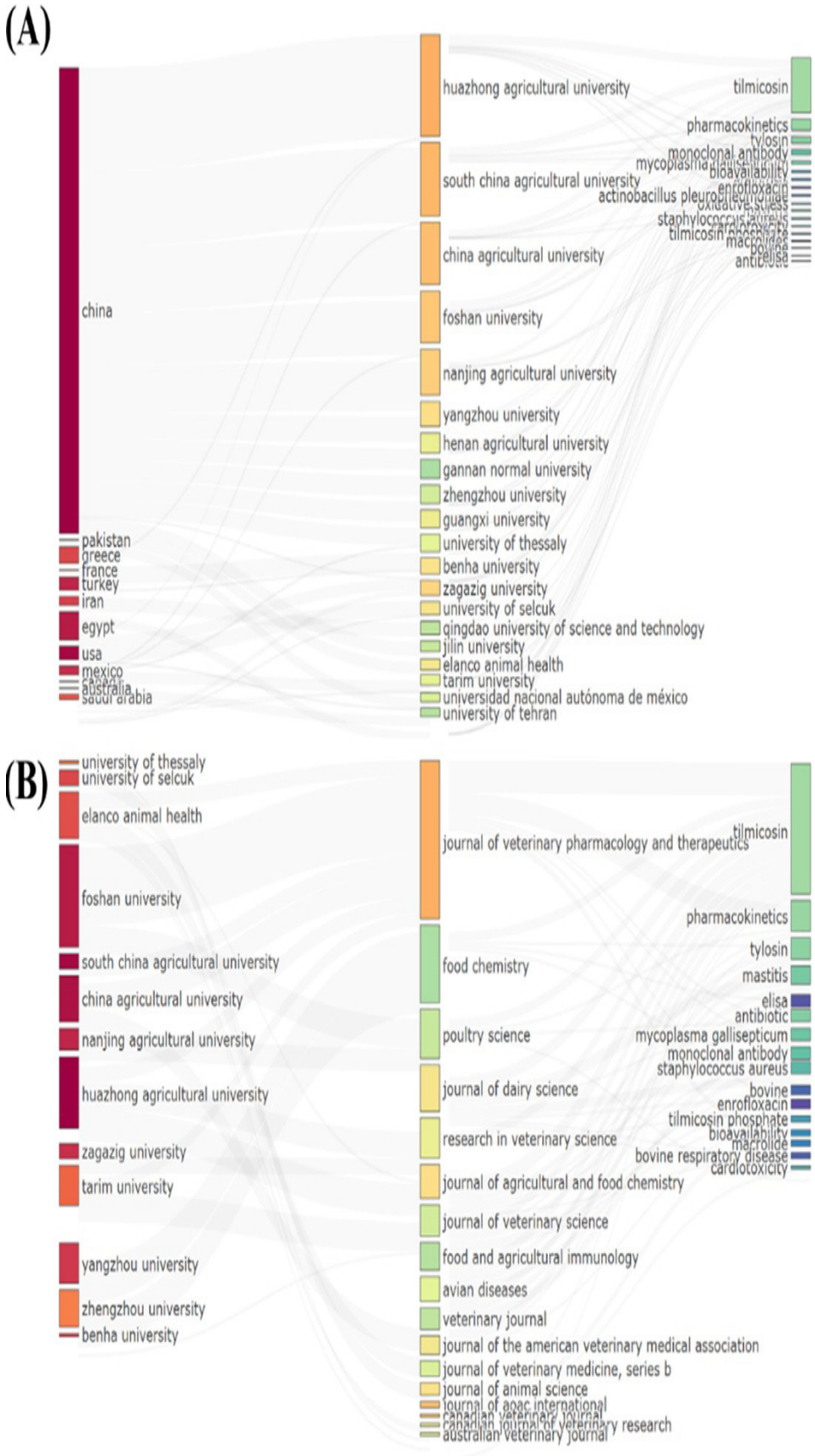

Figure 8: Relationship among countries, institutions, sources, and research topics of tilmicosin research.

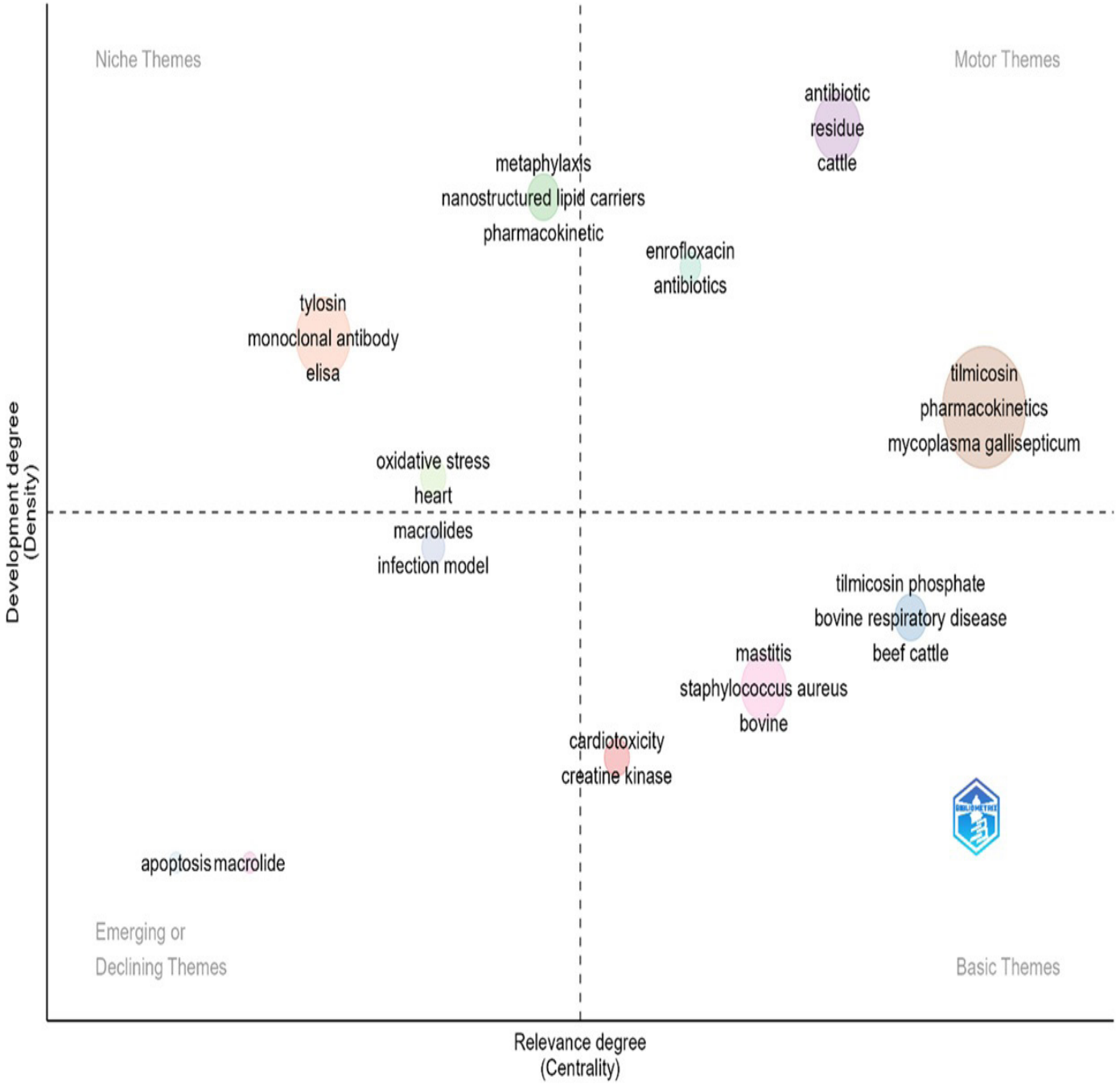

Figure 9: Core, niche, and emerging themes of tilmicosin research.

Thematic clustering and evolution

The co-occurrence network shows tilmicosin centrally clustered with three groups: pharmacology (pharmacokinetics, bioavailability),safety (cardiotoxicity, oxidative stress), and therapeutic terms (mastitis, *Staphylococcus aureus*, macrolides, antibiotic, tylosin, monoclonal antibody). In the overlay map, earlier links around 2010–2012 involve "antibiotic," "mastitis," and "Staphylococcus aureus," whereas later developments after 2014–2018 emphasize pharmacokinetics, bioavailability, monoclonal antibody (median 2016), oxidative stress , and cardiotoxicity, illustrating progressive topic development over time (Figure 10).

DISCUSSION

Our bibliometric analysis shows that tilmicosin research has grown from a niche field into a diverse, globally distributed area over nearly four decades. Although the total number of publications is modest compared to broader antibiotic research, output has clearly increased in recent years, peaking around 2019–2020 and reaching higher levels in 2024.

Chinese institutions dominate the field, reflecting the country's position as the world's largest livestock producer and the importance of managing respiratory diseases

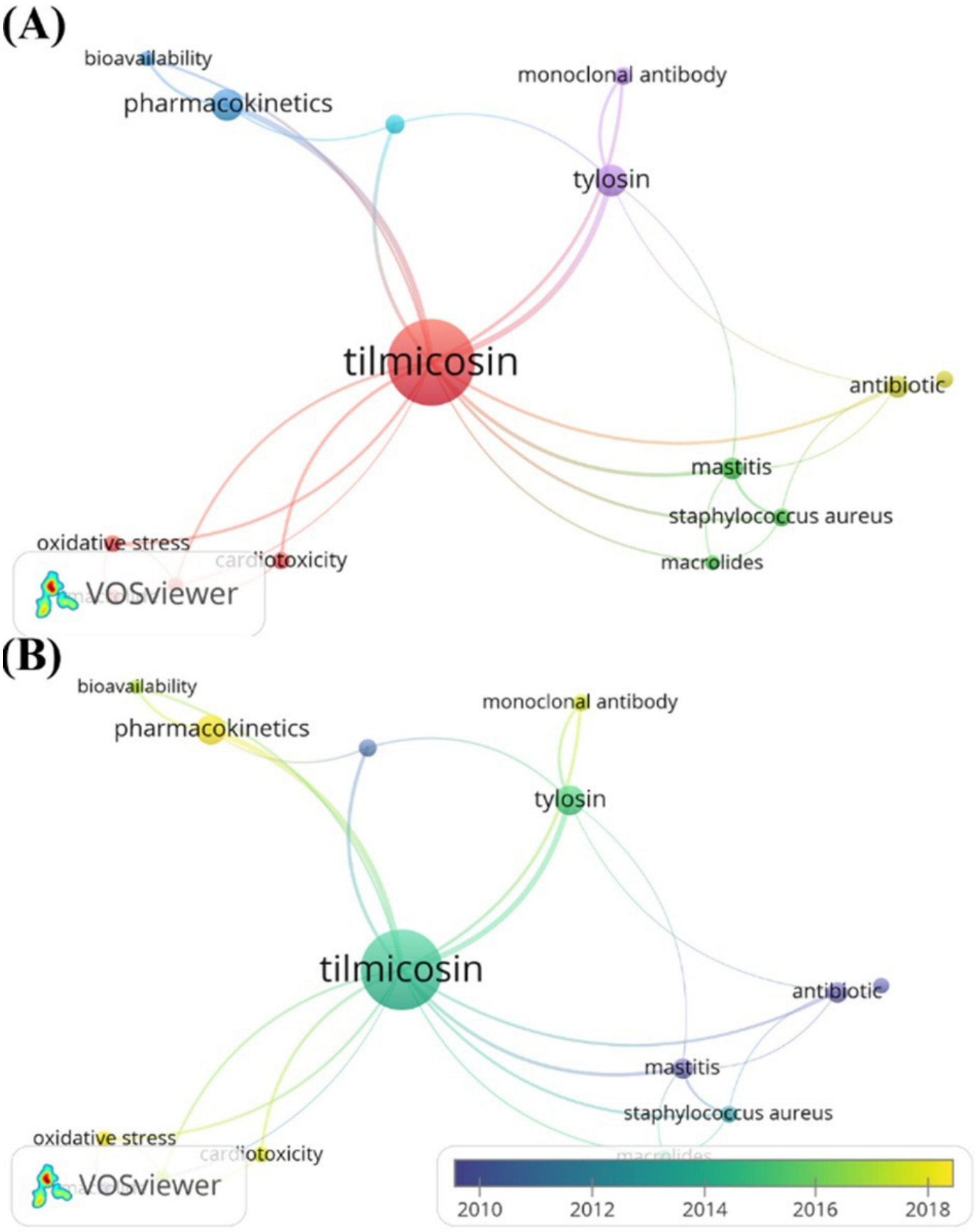

Figure 10: Thematic clustering and evolution of tilmicosin research.

(Qiang *et al*., 2025; Zhou *et al*., 2024). Chinese authors contribute a large share of manuscripts, and affiliations are heavily concentrated in China, highlighting tilmicosin's relevance in intensive animal production regions. Limited international collaborations, such as USA–Canada and Egypt–Saudi Arabia partnerships, reflects the collaboration

on livestock and veterinary aspects.

Thematic focus has shifted from early pharmacokinetic and efficacy studies to investigations of cardiotoxicity, oxidative stress, and antimicrobial resistance. This implies concerns over toxicity of tilmicosin and the concerns from increasing antimicrobial resistance (Vinayamohan *et al*., 2022).

Our findings align with broader trends in veterinary pharmacology while underscoring the unique trajectory of tilmicosin research. Chinese institutions dominated, contributing 27.9% of publications, followed by the USA at 6.7%. These findings coincides with previous reports on gut health analysis (China 24.7%, USA 17.2%) (Colombino *et al*., 2021). This reflects China's leading role in veterinary products. The geographic pattern differs from aminoglycoside research, where the USA led (28.4%), several European countries and Australia contributed 10.1%, and China (6.9%) (Zhao *et al*., 2025). This may be because aminoglycosides have broader clinical applications in both human and veterinary medicine, whereas tilmicosin's exclusively veterinary usage in countries with intensive livestock raising. Moreover, 7 out of the 8 most cited papers (Table 2) were produced from single-country research teams, an indication that the tilmicosin high-impact papers were largely the result of prominent national programs rather than multinational consortium. It is, however, worth mentioning that the impactful papers mostly deal with classical topics, such as pharmacokinetics, efficacy and toxicity, that might be inherently less dependent on international collaboration. Potentially, international cooperation could achieve particular benefit in terms of emerging and trans-disciplinary research areas, antimicrobial resistance, environmental impact, as well as novel delivery systems which require wide geographic studies and alignment of regulatory frameworks.

Tilmicosin's 4.96% annual growth rate, modest compared to other veterinary antimicrobials as florfenicol (10.55%) (Naji *et al*., 2025a). International collaboration remains limited, with only 12.38% of tilmicosin publications involving multinational authorship, contrasting with 57% in antimicrobial stewardship research (Sweileh, 2021). Minimal USA–Canada partnerships and limited Chinese engagement suggest missed opportunities. Uzabaci *et al*. (2025) found that the USA produced 48% of the top 100-cited veterinary articles, highlighting how collaboration enhances visibility (Uzabaci, 2025), a pattern not yet evident in tilmicosin research. Tilmicosin publications concentrate in the Journal of Veterinary Pharmacology and Therapeutics, consistent with the scope of the journal, which focuses on pharmacokinetics and applications in veterinary practice. Unlike statistical time-series model, the reported annual growth was expressed in the form of descriptive exponential growth trend. Since the general low annual scientific production, the interpretation of potential publication peak in 2024 should be approached with caution as annual increase may also represent random fluctuation rather than actual structural increase.

The shift from traditional pharmacological studies to research on safety and resistance has important implications for veterinary practice and public health. The focus on cardiotoxicity, oxidative stress, and apoptosis highlights growing awareness of tilmicosin's adverse effects, which is crucial for refining dosing and risk assessments. Research on nanoparticles, particularly solid lipid nanoparticles for improved drug delivery, offers innovative strategies to address antimicrobial resistance while reducing environmental impact (Wang *et al*., 2012).

The presence of Chinese institutions in research on tilmicosin is related to known facts. Indeed, it is only to be expected that the country with the largest livestock sector of the globe, accounting for almost one-fifth of the demand for animal protein worldwide, would be engaged in intensive and ongoing research activities on veterinary pharmaceuticals (Shi *et al*., 2023). Hence, the mostly single-country 88 publications with a corresponding author affiliated to an institution located in China should not be seen as a coincidence, but rather as the result of investment on animal health, antimicrobial research and development, and regulatory science for an extended period. This has been the case in other veterinary antimicrobials, streptomycin (Naji *et al*., 2026) and florfenicol (Naji *et al*., 2025b) in particular, indicating continuity rather than a single episode. It is also worth mentioning that the bibliometric studies on gut health and antimicrobials in veterinary medicine identify China as the top contributor worldwide (Colombino *et al*., 2021), an outcome clearly congruent with the country hierarchies found on tilmicosin study. These calculations are purely applied to veterinary specific drugs. However, a larger look at aminoglycosides in general would find the diminished contribution of China, which occupies the 6th position worldwide (Zhao *et al*., 2025). This is ultimately due to the wide applicability of aminoglycosides for both human and veterinary practices and not limited to veterinary practice as in the case of tilmicosin.

Nanostructured lipid carriers appeared to be a niche theme, meaning that despite the good technological development (Wen *et al*., 2021; Zhang *et al*., 2020), this subject is poorly engaged in the tilmicosin literature. On the other hand, pharmacokinetics was pointed out as a motor theme related to dose monitoring, safety, residues and the terms of approval of the use in food animals (Chen *et al*., 2023; Sun

et al., 2026; Yan *et al*., 2023), Zhang *et al*., 2022). The fact that nanostructured lipid carriers are still a niche means a loss in translation of promising nanodelivery systems that did not evolve to large-scale clinical trials or regulatory approval for food animals. This loss in translation could be overcome with the collaboration of the different areas that should join formulation science with field trials, residues and antimicrobial stewardship studies.

Our study has various methodological advantages. We used Scopus, a well-curated database, to minimize selection bias and cover international peer-reviewed literature. Only main research publications were included, excluding biased reviews and conference proceedings, improving citation metrics. However, important limitations warrant acknowledgment. Restricting our search to English-language publications may have underrepresented research from non-Anglophone countries, particularly those with significant livestock sectors like Brazil, Russia, and China.

CONCLUSIONS

This bibliometric analysis provides the first comprehensive quantitative synthesis of tilmicosin research spanning 1988-2025, revealing a field transitioning from basic pharmacology topics toward complex safety and resistance investigations. The geographic concentration in China and limited international collaboration suggest opportunities for enhanced antimicrobial knowledge complementation. The thematic shift toward antimicrobial resistance, cardiotoxicity, and novel delivery systems positions tilmicosin research at the intersection of veterinary medicine, environmental science, and public health. Future studies should investigate tilmicosin toxicity in animal species, especially less-studied animals as camels. In addition, food residues and their effect on the heart of humans consuming animal products need to be investigated.

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NOVELTY STATEMENT

This study is the first comprehensive bibliometric analysis of tilmicosin research globally. It offers quantitative values over the conventional descriptive reviews. The fragmented previous tilmicosin research is integrated and revealed the pattern shift in the research themes, specifically from classical areas of research such as pharmacokinetics and therapeutic efficacy towards new challenges like cardiotoxicity, oxidative stress, and antimicrobial resistance, as well as innovative applications such as smart delivery systems. Moreover, it raises important concerns and identifies considerable knowledge gaps that need to be addressed by researchers, such as the need for more international collaborations and exploration of the use of the drug in non-traditional species.

AUTHOR'S CONTRIBUTION

Conceptualization: BF, AA, BA, IA, SM, YK, MK. Data curation: SM, MK. Formal analysis: BF, AA. Funding acquisition: MK. Investigation: IA. Methodology: SM, MK. Project administration: BA. Resources: MK. Software: MK. Writing original draft: MK. Writing review and editing: BF, AA, BA, IA, SM, YK.

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Ethical approval

Not applicable.

Informed consent statement

Not applicable.

Data

Data can be requested from the corresponding author upon reasonable request.

Generative AI and AI assisted technology statement

The authors declare that no generative AI and AI assisted technology was used in the creation of this manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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