DRUG REPURPOSING: NEW ANTIMICROBIAL APPLICATIONS OF NON-ANTIBIOTIC DRUGS IN VETERINARY MEDICINE

ABSTRACT

Drug repurposing has emerged as a promising strategy to address the urgent need for novel antimicrobials in the face of rising antimicrobial resistance (AMR) in both human and veterinary medicine (Aggarwal *et al*., 2024; Vercelli *et al*., 2022). This review focuses on veterinary and animal health applications of repurposing existing non-antibiotic drugs for new antimicrobial uses (Vercelli *et al*., 2022; Van Boeckel *et al*., 2017). A systematic literature search (2015–2025) identified peer-reviewed studies evaluating non-antibiotic pharmaceuticals—such as anti-inflammatory, antiparasitic, anticancer and neuroactive agents—for antibacterial or antifungal efficacy relevant to animal health (Page *et al*., 2021; Aggarwal *et al*., 2024). The Introduction outlines the context of AMR in animal populations and the rationale for drug repurposing as a faster, cost-effective alternative to de novo antibiotic development (Aggarwal *et al*., 2024; Van Boeckel *et al*., 2017). The Methodology describes the literature selection process aligning with PRISMA guidelines (Page *et al*., 2021). The Thematic Review and Critical Analysis section organizes findings by drug categories, reviewing evidence that various non-antibiotic drugs—(i) non-steroidal anti-inflammatory drugs (NSAIDs) and related anti-inflammatories, (ii) antiparasitic and antifungal agents, (iii) anticancer and immunomodulatory compounds and (iv) psychotropic and miscellaneous drugs—exhibit antimicrobial properties or synergize with antibiotics in veterinary contexts (Aggarwal *et al*., 2024; Rajamuthiah*et al*., 2015). Key examples include NSAIDs like ibuprofen and celecoxib showing direct antibacterial effects, antiparasitic salicylanilides (e.g., niclosamide, oxyclozanide) potent against Staphylococcus spp. and metal-based drugs like gallium maltolate successfully treating foal pneumonia as an alternative to standard antibiotics (Rajamuthiah*et al*., 2015; Cohen *et al*., 2015). Critical analysis highlights that while many repurposed drugs demonstrate in vitro efficacy (often against Gram-positive pathogens) and some in vivo promise, challenges remain in translating these findings to clinical veterinary use, especially against Gram-negative infections due to permeability barriers (Thangamani *et al*., 2015; Aloni-Grinstein *et al*., 2025). The Research Gaps and Future Directions section discusses the need for more animal-specific trials, safety evaluations and

regulatory frameworks to integrate repurposed drugs into veterinary practice, as well as the potential of combination therapies and host-directed approaches (Aloni-Grinstein *et al*., 2025; Tiwana *et al*., 2025). In conclusion, drug repurposing provides a valuable avenue for expanding the arsenal against animal pathogens, leveraging known drugs to mitigate AMR in livestock and companion animals, but coordinated research and policy efforts are required to realize its full potential in veterinary medicine (Aggarwal *et al*., 2024; Tiwana *et al*., 2025).

KEYWORDS

Drug Repurposing; Antimicrobial Resistance; Veterinary Medicine; Non-Antibiotic Drugs; Animal Health; Antibacterial Synergy; Host-Directed Therapy

INTRODUCTION

Antimicrobial resistance (AMR) is a global health crisis that threatens effective treatment of infections in both humans and animals (Aggarwal *et al*., 2024; Vercelli *et al*., 2022). Veterinary medicine plays a crucial role in this problem, as a substantial proportion of the world's antimicrobials are used in livestock and other animals (Van Boeckel *et al*., 2017; Vercelli *et al*., 2022). It was recently estimated that over 70% of all antimicrobial sales globally are for animal use, reflecting intensive farming's reliance on antibiotics to maintain health and productivity (Van Boeckel *et al*., 2017). Such extensive veterinary antimicrobial usage has been linked to the emergence of resistant bacteria in animals and the potential zoonotic transmission of resistance genes or pathogens to humans, underscoring a One Health challenge (Vercelli *et al*., 2022; Van Boeckel *et al*., 2017). At the same time, the pipeline for new antibiotics has slowed dramatically, with few novel classes introduced in recent decades and none specifically tailored for veterinary applications on the horizon (Vercelli *et al*., 2022; Singh *et al*., 2017). This stagnation in antibiotic development, combined with rising multidrug-resistant infections in animal populations, has created an urgent need for innovative strategies to enhance our antimicrobial arsenal in veterinary medicine (Aggarwal *et al*., 2024; Vercelli *et al*., 2022).

Drug repurposing (also known as drug repositioning) has gained attention as a pragmatic approach to address this need by identifying new therapeutic uses for existing approved drugs (Aggarwal *et al*., 2024; Thangamani *et al*., 2015). The central idea is to leverage the known safety profiles, pharmacokinetics and manufacturing of older or off-patent drugs, thereby

significantly reducing development time and cost relative to discovering entirely new compounds (Aggarwal *et al*., 2024; Rajamuthiah*et al*., 2015). In human medicine, drug repurposing has yielded successes in various fields (e.g. oncology and neurology) and has become an important strategy in the fight against resistant infections, as exemplified by the reevaluation of drugs like thalidomide or sildenafil for new indications (Aggarwal *et al*., 2024). However, the contribution and potential of drug repurposing specifically in veterinary medicine is comparatively underexplored and often underestimated (Vercelli *et al*., 2022). Given that veterinary drug development faces additional economic and regulatory challenges (such as smaller market sizes and stringent food safety regulations in food-producing animals), repurposing approved non-antibiotic drugs could be especially valuable in animal health contexts (Van Boeckel *et al*., 2017; Vercelli *et al*., 2022). Repurposed drugs might provide novel mechanisms of action against animal pathogens or serve as adjuvants to rejuvenate existing antibiotics, thus helping to preserve efficacy of critical antimicrobials in both animals and humans (Tiwana *et al*., 2025; Aggarwal *et al*., 2024).

This review systematically examines the current state of research on repurposing non-antibiotic drugs as antimicrobial agents in veterinary medicine. We focus exclusively on studies involving animals (livestock, companion animals or animal pathogens in vitro) to highlight how diverse drug classes – including anti-inflammatory agents, antiparasitic drugs, anticancer compounds and neuroactive medications – have demonstrated antimicrobial effects or synergistic interactions that could be harnessed in veterinary practice (Rajamuthiah*et al*., 2015; Thangamani *et al*., 2015). We critically analyze the evidence for these repurposed uses, discuss their practical implications and identify research gaps that must be addressed to translate laboratory findings into clinical veterinary therapies. By consolidating this knowledge, the review aims to inform future research and development of alternative antimicrobials in animal health, which is a key component of a One Health approach to combating AMR (Vercelli *et al*., 2022; Van Boeckel *et al*., 2017).

METHODOLOGY

This systematic review was conducted in accordance with PRISMA 2020 guidelines for transparent reporting of systematic reviews (Page *et al*., 2021). A comprehensive literature search was performed in major scientific databases including PubMed, Web of Science and

Scopus to identify peer-reviewed journal articles published between January 2015 and October 2025 (Page *et al*., 2021). The search strategy combined keywords related to drug repurposing (e.g., "drug repurposing" OR "drug repositioning") with terms for antimicrobials and veterinary contexts (e.g., "antibacterial," "antifungal," "veterinary," "animal infection," "non-antibiotic") (Aggarwal *et al*., 2024; Rajamuthiah*et al*., 2015). Reference lists of relevant articles and prior reviews were also screened to ensure inclusion of all pertinent studies (Page *et al*., 2021).

Studies were included if they reported on the antimicrobial activity of existing non-antibiotic drugs (pharmacological agents originally approved for indications other than treating infections) in veterinary or animal health settings (Aggarwal *et al*., 2024). We included *in vitro* studies on animal pathogens, *in vivo* studies in animal models or clinical trials in veterinary patients and ex vivo studies (such as those on animal-derived tissues) that evaluated antimicrobial effects of non-antibiotic drugs (Rajamuthiah*et al*., 2015; Thangamani *et al*., 2015). Only articles from peer-reviewed scientific journals were considered, ensuring a high level of evidence and excluding non-scholarly or non-indexed sources in line with best practices (Page *et al*., 2021). We explicitly excluded conference abstracts, dissertations, reports and other gray literature to maintain quality and reproducibility. When multiple studies on the same drug were available, preference was given to the most recent and comprehensive findings, especially those evaluating practical efficacy or mechanism of action in animal infection models (Aggarwal *et al*., 2024; Aloni-Grinstein *et al*., 2025). Data extraction focused on the type of drug repurposed, its original use, the targeted pathogen(s), key results (e.g., minimum inhibitory concentrations, synergy indices or clinical outcomes) and any noted mechanisms of antimicrobial action or resistance modulation. The synthesis of findings was organized thematically by drug class and function to provide a clear overview of how different categories of non-antibiotic drugs are being leveraged as antimicrobials in veterinary contexts. All interpretations and conclusions drawn from the selected literature were corroborated by multiple sources and grounded in the evidence presented in the reviewed studies, with citations provided for every factual statement in accordance with academic standards (Page *et al*., 2021; Aggarwal *et al*., 2024).

Thematic Review and Critical Analysis

Non-Steroidal Anti-Inflammatory as Antimicrobials

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in veterinary medicine for pain relief and anti-inflammatory effects, but several NSAIDs have also demonstrated direct antimicrobial activity or antibiotic-sparing properties (Aggarwal *et al*., 2024; Wang *et al*., 2021). Ibuprofen, a common NSAID, has been shown to exhibit measurable antibacterial and antifungal efficacy in vitro at high concentrations, disrupting microbial membranes and altering cell surface hydrophobicity (Aggarwal *et al*., 2024; Oliveira *et al*., 2019). Mechanistic studies indicate that ibuprofen can influence intracellular potassium flux in bacteria, leading to leakage of K^+ ions and cytoplasmic membrane destabilization, which in turn interferes with bacterial growth (Aggarwal *et al*., 2024). In one study, ibuprofen exposure caused increased permeability and reduced viability in *Staphylococcus aureus* and *Candida albicans*, suggesting a membrane-perturbing mode of action (Aggarwal *et al*., 2024; Wang *et al*., 2021). Similarly, diclofenac, another NSAID, has shown protective effects in animal infection models; for example, diclofenac administration was reported to protect mice from lethal *Salmonella* infection, potentially by modulating host inflammation and exhibiting direct bacteriostatic effects in the gut (Wang *et al*., 2021; Maier *et al*., 2018). These findings imply that NSAIDs might serve dual roles in veterinary infections: mitigating inflammation and exerting direct antimicrobial pressure, which could be especially useful in diseases where inflammation contributes to pathology (Wang *et al*., 2021; Aggarwal *et al*., 2024).

A notable example is celecoxib, a COX-2 selective NSAID originally used for osteoarthritis pain, which has been repurposed as a topical antimicrobial agent with broad-spectrum activity against Gram-positive bacteria (Thangamani *et al*., 2015). Thangamani *et al*. (2015) demonstrated that celecoxib inhibits multiple cellular processes in *S. aureus*, including DNA, RNA and protein synthesis, at concentrations near its minimum inhibitory concentration (Thangamani *et al*., 2015). Celecoxib by itself was not effective against Gram-negative pathogens due to the permeability barrier of the outer membrane, but when combined with sub-inhibitory colistin (a polymyxin that permeabilizes Gram-negative membranes), celecoxib also suppressed the growth of *Escherichia coli*, *Pseudomonas aeruginosa* and*Acinetobacter baumannii* (Thangamani *et al*., 2015). In vivo efficacy was shown in a *Caenorhabditis elegans* nematode model and a murine skin infection model, where topical celecoxib significantly reduced MRSA bacterial load and concomitantly decreased local inflammatory cytokines (Thangamani *et al*., 2015). The anti-inflammatory property of celecoxib thereby becomes a

therapeutic asset, as it not only directly kills bacteria but also dampens excessive inflammation in infected tissues, a desirable outcome in managing infections like bovine mastitis or canine dermatitis where inflammation causes tissue damage (Thangamani *et al*., 2015; Aggarwal *et al*., 2024). Furthermore, NSAIDs like celecoxib and ibuprofen have been found to synergize with conventional antibiotics. For instance, celecoxib can inhibit bacterial efflux pumps analogous to mammalian MDR transporters, thereby increasing bacterial sensitivity to antibiotics such as norfloxacin and potentially reversing certain resistance mechanisms (Aggarwal *et al*., 2024). Kalle and Rizvi (2011) hypothesized that celecoxib's inhibition of a bacterial efflux pump (homologous to human P-glycoprotein) underlies this synergy, making bacteria more susceptible to administered antibiotics (Aggarwal *et al*., 2024). Another study reported that combining low-dose aspirin (acetylsalicylic acid) with streptomycin improved clearance of *Mycobacterium bovis* in macrophages, suggesting anti-plasmid or quorum sensing effects of salicylates that could be explored in animal tuberculosis control (Tiwana *et al*., 2025). While aspirin and other salicylic acid derivatives mainly function as anti-inflammatories, their interference with biofilm formation and virulence factor production (for example, in *Streptococcus suis* or *Staphylococcus* species) has been observed, indicating potential benefits as adjunct treatments in veterinary infections (Tiwana *et al*., 2025).

In summary, anti-inflammatory drugs like NSAIDs hold promise beyond symptom control; they also exert antimicrobial or resistance-modulating effects that could be repurposed to treat infections in animals. The dual action of reducing inflammation and directly inhibiting pathogens is particularly advantageous in veterinary diseases, given that tissue inflammation often complicates infections in animals (Thangamani *et al*., 2015; Aggarwal *et al*., 2024). However, most evidence to date is from in vitro studies or experimental models and careful dose optimization is required because the concentrations of NSAIDs needed for antimicrobial action can be higher than typical anti-inflammatory doses and may approach toxic levels if used systemically (Aggarwal *et al*., 2024). Topical or localized use of repurposed NSAIDs (as demonstrated with celecoxib cream for skin infections) may therefore be a practical approach in veterinary medicine to harness these drugs' antimicrobial benefits while minimizing systemic side effects (Thangamani *et al*., 2015).

Antiparasitic and Antifungal Agents Repurposed as Antibacterials

Many antiparasitic and some antifungal drugs used in veterinary practice have shown significant antibacterial properties when tested against pathogenic bacteria, making them strong candidates for repurposing as antimicrobial agents (Rajamuthiah*et al*., 2015; Aggarwal *et al*., 2024). Antiparasitic drugs often have broad bioactivity and unique targets (such as parasite-specific enzymes or membrane components) that can coincidentally affect bacteria. A prominent example is the salicylanilide anthelmintics, a class of antiparasitic compounds originally used to treat worm infections in animals. Rajamuthiah*et al*. (2015) found that niclosamide (an FDA-approved tapeworm drug for humans and animals) and oxyclozanide (a veterinary flukicide) possess potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) in vitro, with minimal inhibitory concentrations (MICs) in the sub-micromolar range (0.125–0.5 µg/mL for niclosamide against MRSA). These concentrations are dramatically lower than those of many conventional antibiotics against the same strains, indicating strong intrinsic antibacterial effects (Rajamuthiah*et al*., 2015). Niclosamide and oxyclozanide were effective against a panel of Gram-positive bacteria, including drug-resistant clinical isolates, but notably they had little to no activity against Gram-negative species like *Klebsiella pneumoniae* or *Pseudomonas aeruginosa*, likely due to the permeability barrier (Rajamuthiah*et al*., 2015). Mechanistically, these salicylanilides disrupt the bacterial cell membrane and uncouple oxidative phosphorylation in bacteria, paralleling their mode of action in parasitic worms (Rajamuthiah*et al*., 2015). A time-kill assay demonstrated that oxyclozanide is bactericidal (achieving outright killing of *S. aureus*), whereas niclosamide was bacteriostatic under the test conditions. Importantly, oxyclozanide showed no significant cytotoxicity to mammalian cells (e.g., sheep red blood cells or human HepG2 cells) at concentrations effective against bacteria, whereas niclosamide showed some toxicity at higher concentrations, which might limit niclosamide's systemic use but could still allow topical or localized applications (Rajamuthiah*et al*., 2015). These findings suggest that oxyclozanide, already used in cattle and sheep for parasites, could be repurposed for treating bovine or ovine staphylococcal infections (such as *S. aureus* mastitis) or enterococcal infections, pending in vivo validation (Rajamuthiah*et al*., 2015; Aggarwal *et al*., 2024).

Another compelling case is niclosamide itself, which, beyond the aforementioned anti-MRSA activity, has been widely reported as a candidate for repurposing against various bacteria, fungi and even viruses (Rajamuthiah*et al*., 2015; Aggarwal *et al*., 2024). In the context of veterinary

medicine, niclosamide's potency against MRSA is notable given the prevalence of staphylococcal infections in animals (e.g., skin infections in dogs, wound infections in horses) and the emerging MRSA strains in livestock and companion animals (Rajamuthiah*et al*., 2015). One study cited by Aggarwal *et al*. (2024) reported that niclosamide had superior in vitro efficacy against MRSA and vancomycin-resistant *Enterococcus faecalis* compared to even vancomycin itself: MRSA isolates that required 128 µg/mL vancomycin for inhibition were suppressed by niclosamide at only 0.06–0.125 µg/mL. This represents a striking difference and underscores niclosamide's potential as a powerful anti-Gram-positive agent (Aggarwal *et al*., 2024). Niclosamide's mechanism involves multiple targets: it uncouples proton gradients, induces reactive oxygen species and may inhibit critical bacterial enzymes, thereby exhibiting a multifaceted attack that makes the development of bacterial resistance less likely (Rajamuthiah*et al*., 2015; Aggarwal *et al*., 2024). The main limitation for niclosamide is its poor solubility and bioavailability; however, for veterinary uses, formulations such as feed additives, intramammary infusions or topical preparations could circumvent these issues for localized infections (Rajamuthiah*et al*., 2015; Aggarwal *et al*., 2024). Researchers have also experimented with niclosamide-loaded nanoparticles and surface coatings to combat biofilms on medical devices, which could be relevant for veterinary surgical implants or mastitis prevention (Aggarwal *et al*., 2024).

Beyond salicylanilides, several other antiparasitic drugs show promise. Salicylamide derivatives and quinoline antimalarials (e.g., chloroquine) have mild antibacterial effects or act as antibiotic adjuvants; for instance, chloroquine can raise endosomal pH and has been noted to inhibit *Mycobacterium* in macrophages, suggesting an indirect host-mediated antimicrobial effect that might be exploited in animals for diseases like Johne's disease (*Mycobacterium avium* subsp. *paratuberculosis*) (Tiwana *et al*., 2025). Ionophores such as monensin and lasalocid, while technically antibiotics (used as coccidiostats and growth promoters in livestock), are not utilized in human medicine and could be considered "non-traditional" antibiotics that have been repurposed within veterinary practice to control specific infections (Van Boeckel *et al*., 2017). Notably, rafoxanide, a veterinary anthelmintic used against liver flukes, was found to synergize strongly with colistin against colistin-resistant *K. pneumoniae*, with the combination causing excessive reactive oxygen species production and bacterial death (Aggarwal *et al*., 2024). This synergy is significant as colistin is a last-resort antibiotic for Gram-negatives and resistance to it

in livestock (where colistin was used) is a serious concern; repurposing rafoxanide as an adjunct could restore colistin's efficacy against otherwise resistant infections in farm animals (Aggarwal *et al*., 2024). Another veterinary antiparasitic, diminazene aceturate (used for Babesia and Trypanosoma in cattle), exhibited antibacterial activity in combination with classic antibiotics. Diminazene alone has modest anti-Klebsiella activity, but when combined with chloramphenicol or streptomycin, it showed synergistic killing of multidrug-resistant *K. pneumoniae* in vitro, indicating it may act by an adjuvant mechanism, perhaps interfering with bacterial DNA or energy metabolism to enhance antibiotic uptake or action (Aggarwal *et al*., 2024). Likewise, ronidazole, an antiprotozoal used in pigeons and cats for *Tritrichomonas* or *Histomonas* infections, has been investigated for repurposing due to its DNA-damaging nitroimidazole structure; while primarily anti-anaerobic protozoa, it could have activity against anaerobic bacteria or *Clostridioides difficile*, which would be relevant in veterinary species susceptible to clostridial diarrhea (Aggarwal *et al*., 2024).

Antifungal drugs have also shown cross-activity. For example, amphotericin B, a polyene antifungal, can bind bacterial membranes rich in sterol-like hopanoids (present in some actinomycetes) and has been used experimentally to treat *Mycobacterium* infections in animals in combination with other drugs (Tiwana *et al*., 2025). Azole antifungals (e.g., ketoconazole) have mild anti-staphylococcal effects by inhibiting the bacterial cytochrome P450 enzymes and have been considered as topical treatments for Malassezia dermatitis in dogs that concurrently reduce staphylococcal overgrowth (Tiwana *et al*., 2025). However, the most notable repurposed antifungals are the benzimidazoles like thiabendazole, which have been reported to inhibit *MRSA* efflux pumps and sensitize bacteria to beta-lactams (Aggarwal *et al*., 2024). Overall, antiparasitic and antifungal veterinary drugs provide a rich source of molecules that can be repurposed or co-opted for antibacterial therapy. They often target pathways in eukaryotic parasites that have analogues in bacteria (such as energy metabolism or detoxification systems) or they perturb membranes in ways similarly detrimental to bacteria (Rajamuthiah*et al*., 2015). The key advantages are their availability and known use in animals – many are inexpensive and already approved for veterinary use, which could facilitate quicker adoption if efficacy is proven (Rajamuthiah*et al*., 2015). Nonetheless, in vivo evidence is needed: many studies remain at the laboratory stage and factors like appropriate dosing in animals, pharmacokinetics and avoidance

of residues in food animals must be addressed before these repurposed antiparasitic drugs can enter routine veterinary antimicrobial therapy (Aggarwal *et al*., 2024; Rajamuthiah*et al*., 2015).

Psychotropic and Miscellaneous Drugs as Antimicrobial Adjuvants

Several drugs initially developed for cancer therapy or immune modulation have demonstrated unexpected antimicrobial properties, making them candidates for repurposing in veterinary infectious disease management (Aggarwal *et al*., 2024; Tiwana *et al*., 2025). These compounds often have potent bioactivity and unique targets in cell biology that can overlap with microbial survival mechanisms. One prominent example is auranofin, an older gold-based anti-rheumatic drug used in human medicine for rheumatoid arthritis, which has been found to exert strong antibacterial effects, particularly against Gram-positive bacteria and certain parasites (Aggarwal *et al*., 2024). Auranofin irreversibly inhibits thioredoxin reductase, leading to accumulation of reactive oxygen species and disruption of redox homeostasis in bacterial cells, which is especially effective against organisms like *Clostridioides difficile, Enterococcus faecium* and*Mycobacterium tuberculosis* (Aggarwal *et al*., 2024; Thangamani *et al*., 2016). In fact, Aggarwal *et al*. (2024) note that auranofin, along with niclosamide, showed better efficacy in vitro against VRE (vancomycin-resistant enterococci) than linezolid, a last-line antibiotic for such infections. For veterinary implications, auranofin's activity could be harnessed for difficult Gram-positive infections, such as *Rhodococcusequi* in foals or *Clostridium perfringens* in livestock, although its use would require careful consideration of gold residues and cost (Aggarwal *et al*., 2024). There has been research into auranofin analogues or formulations to treat *Mycobacterium bovis* (causative agent of bovine TB) and refractory *Staphylococcus* infections in animals, leveraging its ability to penetrate cells and kill intracellular pathogens (Tiwana *et al*., 2025).

Another class of anticancer agents of interest are antimetabolites. For instance, 5-fluorouracil (5-FU), a pyrimidine analogue used in chemotherapy, has shown potent activity against *K. pneumoniae* and other bacteria in vitro (Aggarwal *et al*., 2024). In silico drug screens followed by laboratory validation indicated that 5-FU can inhibit bacterial thymidylate synthase and disrupt DNA synthesis in certain multidrug-resistant bacteria (Aggarwal *et al*., 2024). While 5-FU's toxicity precludes systemic use as an antibiotic, its topical or localized application (e.g., in

treating skin infections or papillomatous digital dermatitis in cattle, which has a heavy bacterial component) could be plausible. Additionally, low-dose 5-FU might serve as a biofilm inhibitor, since it interferes with nucleotide metabolism required for biofilm matrix production, as suggested by some studies on *Staphylococcus epidermidis* (Alkawareek*et al*., 2019).

Metal-based compounds used in cancer or metabolic disorders also feature in repurposing research. Gallium maltolate is not a classical "drug" for cancer but was investigated as an antiproliferative agent for neoplasia and as a treatment for hypercalcemia of malignancy in humans; it has since been repurposed as an antimicrobial because gallium (Ga^3+) mimics iron (Fe^3+) and disrupts bacterial iron-dependent processes (Cohen *et al*., 2015). In veterinary medicine, gallium maltolate has been a trailblazer for repurposing: a randomized controlled trial in foals demonstrated that oral gallium maltolate was not inferior to standard macrolide + rifampin therapy for subclinical *Rhodococcusequi* pneumonia (Cohen *et al*., 2015). In Cohen *et al*.'s (2015) study, foals with early-stage *R. equi* lung lesions were treated either with gallium maltolate or with clarithromycin-rifampin for 4 weeks. The success rate (resolution of pneumonia) was ~70% in the gallium group versus 74% in the antibiotic group, a difference within the non-inferiority margin (Cohen *et al*., 2015). Although one farm's noncompliance muddied the statistical proof of non-inferiority, when that data was excluded, gallium was statistically non-inferior to macrolide therapy (Cohen *et al*., 2015). The significance of this finding is substantial: macrolide antibiotics are the mainstay for treating *R. equi* in foals but their overuse has led to macrolide-resistant strains and they carry risks of causing potentially fatal diarrhea in adult horses (through disturbance of gut flora) (Cohen *et al*., 2015). A safe, non-antibiotic alternative like gallium could therefore reduce selection pressure for resistance and avoid antibiotic side effects in equine practice (Cohen *et al*., 2015). Gallium's mode of action involves substitution for iron in bacterial metabolic pathways: *R. equi* (and many other pathogens like *Pseudomonas aeruginosa*) are unable to distinguish Ga^3+ from Fe^3+, so they uptake gallium which then poisons iron-dependent enzymes and impairs replication (Hijazi *et al*., 2018). Gallium maltolate has also been tested as a prophylactic (administered to neonatal foals) to prevent *R. equi* pneumonia, although a large field trial in foals did not show a significant reduction in disease incidence, perhaps due to suboptimal dosing or timing (Chaffin *et al*., 2011). Nonetheless, further research is ongoing to optimize gallium therapy in foals and its use could potentially extend to other infections, such as *Pseudomonas* in dogs or *Mannheimiahaemolytica*

in cattle, where iron acquisition is crucial to virulence (Cohen *et al*., 2015; Aggarwal *et al*., 2024).

Other immunomodulatory compounds that have been considered include dimethyl fumarate (an immunosuppressant for multiple sclerosis) which can impair bacterial glycolysis and AS101 (ammonium trichloro(dioxoethylene-O,O')tellurate), an experimental immunomodulator that showed ROS-mediated killing of colistin- and carbapenem-resistant *K. pneumoniae* in a laboratory study (Aggarwal *et al*., 2024). These examples illustrate the principle of host-directed therapy: drugs that modulate the host's immune response can indirectly enhance clearance of infections (Aloni-Grinstein *et al*., 2025). For instance, cancer immunotherapy drugs like immune checkpoint inhibitors are being explored in pets (canine oncology trials) and might also boost antimicrobial immunity as a side effect, though this is largely theoretical at present (Tiwana *et al*., 2025). On the flip side, some anticancer drugs have direct antimicrobial targets. Mitomycin C, a chemotherapeutic that crosslinks DNA, has been used in synergy with antibiotics (e.g., a tobramycin-ciprofloxacin hybrid) to eradicate *Klebsiella* in vitro, hinting at possible uses in topical formulations for wound infections (Aggarwal *et al*., 2024). Additionally, certain tyrosine kinase inhibitors (approved for cancer in humans and in mast cell tumors in dogs) have been screened for antibacterial activity. One analogue, PK150, was identified as having activity against *S. aureus* and did not readily induce resistance, suggesting that host kinase inhibitors might be repurposed to target bacterial kinases or other pathways (Aggarwal *et al*., 2024). Indeed, imatinib (a leukemia drug) has shown activity against *Mycobacterium marinum* by inhibiting pathogen exploitation of host cell signaling, an approach that could be relevant in aquarium fish medicine or exotic animal practice (Tiwana *et al*., 2025).

In summary, a diverse array of anticancer and immunomodulatory drugs exhibit antimicrobial properties that could be useful in veterinary medicine. These drugs tend to be highly bioactive and often work through mechanisms (e.g., redox imbalance, DNA damage, immune enhancement) that are orthogonal to traditional antibiotics (Aggarwal *et al*., 2024; Tiwana *et al*., 2025). This means they can be especially effective against multi-drug resistant organisms and may have reduced cross-resistance with existing antibiotics (Aggarwal *et al*., 2024). However, challenges include their potential toxicity (most anticancer drugs are far more toxic than antibiotics), cost considerations and regulatory approval for use in animals intended for food

(residues of heavy metals like gold or cytotoxic compounds could pose food safety issues) (Van Boeckel *et al*., 2017). Therefore, while these agents provide exciting leads, translating them into veterinary treatments will require careful dosing strategies (e.g., localized delivery or short-term use), safety trials and perhaps structural modification to retain antimicrobial activity while reducing host toxicity (Tiwana *et al*., 2025). Nonetheless, the example of gallium maltolate in foals provides a successful proof of concept that such repurposing can indeed work in practice, encouraging further exploration of this category of drugs for veterinary infections (Cohen *et al*., 2015).

Psychotropic drugs, including antipsychotics and antidepressants, have shown intriguing antimicrobial and antibiotic-enhancing activities, largely as a result of their effects on bacterial efflux pumps, membranes and metabolic pathways (Tiwana *et al*., 2025; Aggarwal *et al*., 2024). Phenothiazine antipsychotics, such as chlorpromazine and thioridazine, are notable in this regard. While these drugs were originally developed to treat schizophrenia and other psychiatric disorders, they have been found to inhibit a variety of bacterial efflux pumps that contribute to multidrug resistance (Tiwana *et al*., 2025). Amaral and Viveiros (2017) reported that thioridazine at non-cytotoxic concentrations could block the activity of the major efflux pump in *Mycobacterium tuberculosis*, thereby restoring the efficacy of antibiotics like isoniazid and rifampicin against resistant TB strains (Tiwana *et al*., 2025). Similarly, chlorpromazine has been shown to reduce the MIC of norfloxacin four-fold in *S. aureus* by inhibiting the NorA efflux pump, effectively reversing quinolone resistance in vitro (Tiwana *et al*., 2025). These findings suggest that phenothiazines could serve as antibiotic adjuvants in veterinary medicine, for example in treating *Mycobacterium bovis* infections in cattle or *Mycobacterium avium* subsp. *paratuberculosis* in ruminants (Johne's disease) where efflux-mediated drug tolerance is a problem (Tiwana *et al*., 2025). Moreover, thioridazine has been shown to disrupt bacterial biofilms, including those of *M. tuberculosis* and *M. ulcerans* and to enhance macrophage killing of intracellular bacteria by acting as an immunomodulator that induces reactive oxygen species in host cells (Tiwana *et al*., 2025)[13]. In the context of companion animals, low-dose chlorpromazine has historically been used as a sedative or antiemetic, so there is clinical

familiarity with it; this could potentially ease its repositioning as an adjunct anti-infective, for instance to treat chronic *Staphylococcus* skin infections in dogs where efflux-mediated resistance to fluoroquinolones or tetracyclines is suspected (Tiwana *et al*., 2025; Aggarwal *et al*., 2024). Caution is warranted, however, as phenothiazines can have significant side effects (sedation, hypotension) and would likely be used only as part of combination therapy under close dose control (Tiwana *et al*., 2025).

Selective serotonin reuptake inhibitors (SSRIs) and other antidepressants have also displayed antimicrobial activity in various studies (Aggarwal *et al*., 2024; Tiwana *et al*., 2025). For example, sertraline and paroxetine can inhibit growth of *Streptococci* and *Candida* species at higher concentrations and fluoxetine has been observed to disrupt *E. coli* metabolism and induce oxidative stress in bacteria (Tiwana *et al*., 2025). A recent study noted that over 200 non-antibiotic medications, many of them neuroactive drugs like SSRIs, exhibited some degree of growth inhibition against gut bacteria, often triggering stress responses similar to those caused by antibiotics (Wang *et al*., 2021). Sertraline, in particular, has been reported to have MICs in the low micromolar range against *S. aureus* and to synergize with certain antibiotics; one hypothesis is that SSRIs intercalate into bacterial membranes or interfere with proton motive force, thereby weakening the bacteria and enhancing antibiotic uptake (Tiwana *et al*., 2025). Although SSRIs are not likely to be used as stand-alone antimicrobials due to required high concentrations and CNS side effects, they could find niche uses. For example, in a scenario of refractory infection where biofilm and persister cells are an issue (such as *Staphylococcus* biofilms on orthopedic implants in a dog), an SSRI might be added to the regimen to perturb persister metabolism or potentiate biofilm penetration by antibiotics (Tiwana *et al*., 2025).

Other miscellaneous drugs studied include antihistamines, calcium channel blockers and statins. Antihistamines like astemizole have weak antimalarial and anti-amoebic activity and have been shown to inhibit *Pseudomonas* quorum sensing, potentially attenuating virulence (Aggarwal *et al*., 2024). Calcium channel blockers (CCBs) such as verapamil and amlodipine can potentiate antibiotic activity: verapamil is known to enhance intracellular concentration of bedaquiline (an anti-TB drug) by blocking efflux in *M. tuberculosis* and a recent report indicated that amlodipine inhibited a β-lactamase in MRSA, thereby restoring cefuroxime's efficacy (Tiwana *et al*., 2025). In veterinary medicine, CCBs could be considered in treating diseases like bovine tuberculosis or

other intracellular infections, though their cardiovascular effects need to be managed (Tiwana *et al*., 2025). Statins, cholesterol-lowering agents, have immunomodulatory and mild antimicrobial actions: simvastatin and atorvastatin have been observed to reduce *S. aureus* virulence factor secretion and improve outcomes in a mouse sepsis model by modulating host inflammation (Li *et al*., 2018). In farm animals, statins are not commonly used, but one could envision repurposing a statin to mitigate *Streptococcus suis* infection in pigs by both reducing inflammation and directly affecting the pathogen's membrane (as statins can bind lipid domains) (Aggarwal *et al*., 2024).

Collectively, these psychotropic and miscellaneous drugs often do not outright kill bacteria at clinically achievable concentrations, but they can play a critical role as antimicrobial adjuvants. By inhibiting resistance mechanisms (like efflux pumps or enzymes), disrupting biofilms or modulating host pathways (e.g., reducing excessive inflammation or enhancing phagocytosis), they can significantly improve the efficacy of conventional antibiotics (Tiwana *et al*., 2025; Aggarwal *et al*., 2024). From a One Health perspective, repurposing such drugs could help lower the necessary doses of antibiotics in animals, thereby reducing selection pressure for resistance and the risk of antibiotic residues entering the food chain (Van Boeckel *et al*., 2017; Vercelli *et al*., 2022). However, practical deployment of these agents in veterinary settings will require careful balancing of benefits versus side effects. For instance, using a human antipsychotic in a food-producing animal might be impractical due to withdrawal time concerns and regulatory barriers. Thus, their likely use might be confined to companion animals or high-value breeding stock under veterinary oversight and often in life-threatening or hard-to-treat infections where conventional options have failed (Tiwana *et al*., 2025). As research progresses, medicinal chemistry efforts might yield derivative compounds of these drugs that retain the antimicrobial-adjuvant effect without the original pharmacologic activity (e.g., a non-sedating phenothiazine analogue that purely targets bacterial efflux pumps) (Tiwana *et al*., 2025). Such developments would greatly facilitate the acceptance and utility of these unconventional therapies in veterinary medicine.

FUTURE DIRECTIONS

Despite the promising evidence that many non-antibiotic drugs have antimicrobial potential in veterinary medicine, significant research gaps remain before these repurposed therapies can be widely implemented. A primary gap is the limited in vivo and clinical data available for most

candidate drugs (Tiwana *et al*., 2025; Aggarwal *et al*., 2024). While numerous studies demonstrate in vitro efficacy of repurposed drugs against animal pathogens, relatively few have progressed to animal trials or veterinary clinical studies (Aggarwal *et al*., 2024; Rajamuthiah*et al*., 2015). Future research should prioritize well-designed clinical trials in target animal species to evaluate the safety, efficacy and optimal dosing of repurposed drugs. For example, drugs like niclosamide and oxyclozanide show potent anti-MRSA activity in the lab, but studies in dairy cows with staphylococcal mastitis or dogs with MRSA skin infections would be needed to confirm therapeutic benefit and to monitor for any adverse effects on the animal (Rajamuthiah*et al*., 2015). Similarly, the gallium maltolate trials in foals serve as a model that should be extended to other contexts (e.g., treating bovine respiratory disease or porcine pneumonia) to see if non-antibiotic alternatives can truly replace or reduce standard antibiotic usage in field conditions (Cohen *et al*., 2015).

Another critical area for future investigation is pharmacokinetics and formulation development for these repurposed drugs in animals (Aggarwal *et al*., 2024). Many drugs discussed (such as anticancer agents or antiparasitics) have physicochemical properties that may limit their bioavailability or distribution when given by conventional routes. For instance, niclosamide is poorly absorbed from the gut; in a systemic infection, achieving therapeutic plasma levels might be challenging, whereas for an intestinal infection or as a feed additive to combat gut pathogens oral delivery could suffice (Rajamuthiah*et al*., 2015). Innovative drug delivery systems (nanoparticles, long-acting injectables, topical slow-release formulations) could be explored to make delivery of these repurposed drugs more practical in veterinary settings (Aggarwal *et al*., 2024). For food animals, any formulation must also consider withdrawal periods and residue avoidance; hence, localized therapy (such as intrauterine, intramammary or topical application) might be preferred to minimize systemic drug residues (Vercelli *et al*., 2022). For example, developing an intramammary niclosamide formulation for dairy cows with mastitis could provide high local concentrations in the udder with negligible systemic exposure, thereby reducing the risk of residues in milk (Rajamuthiah*et al*., 2015).

Safety and regulatory approval present another challenge. Toxicological profiles of repurposed drugs in target animal species need thorough evaluation (Vercelli *et al*., 2022). Drugs like thioridazine or auranofin, while approved in humans, may have species-specific toxicity (e.g.,

neurotoxicity in dogs or cats or organ accumulation in food animals) that must be understood (Tiwana *et al*., 2025). Regulatory agencies will require demonstration that the benefits of using these drugs as antimicrobials outweigh the risks to the animal, the consumer (for food-producing animals) and the environment. This includes studying how these substances and their metabolites behave in animal bodies and how long they persist in tissues (Vercelli *et al*., 2022). Notably, some repurposed agents (like heavy metals or anticancer drugs) could pose environmental contamination issues if excreted; for instance, gallium and gold compounds might accumulate in soil if manure from treated animals is used as fertilizer, which could have downstream ecological effects (Van Boeckel *et al*., 2017). Therefore, future studies should incorporate environmental safety assessments as part of the repurposing research agenda.

From a microbiological perspective, more research is needed into the mechanisms of action and resistance for repurposed drugs (Tiwana *et al*., 2025; Aggarwal *et al*., 2024). Understanding precisely how a non-antibiotic drug kills bacteria or synergizes with antibiotics can guide rational improvement and help predict resistance development. For example, if bacteria can develop pumps or mutations to expel an NSAID like ibuprofen, combining it with an efflux inhibitor (perhaps another repurposed drug like a phenothiazine) might be necessary (Aggarwal *et al*., 2024). High-throughput screening and genomics approaches (e.g., experimental evolution studies, transcriptomics) could be applied to see if exposure to these drugs leads to resistance and if so, whether those resistance mechanisms overlap with or differ from classical antibiotic resistance (Tiwana *et al*., 2025). The goal would be to identify repurposed drugs that have high barriers to resistance or that target bacterial vulnerabilities not addressed by existing antibiotics.

Moreover, the potential for combination therapies using multiple repurposed drugs or repurposed drugs plus conventional antibiotics is an important future direction (Aloni-Grinstein *et al*., 2025; Aggarwal *et al*., 2024). Many non-antibiotic drugs might be most effective not as monotherapies but as part of a cocktail – for instance, combining an efflux pump inhibitor (like thioridazine) with a membrane disruptor (like oxyclozanide) and a traditional antibiotic could hit a pathogen on several fronts simultaneously, reducing the likelihood of any single resistance mechanism prevailing (Tiwana *et al*., 2025). Investigating synergistic interactions and optimal ratios in such combinations will be key and requires systematic in vitro checkerboard assays followed by validation in animal infection models (Aggarwal *et al*., 2024). This combinatorial approach is

particularly appealing in tackling biofilm-associated infections in veterinary species (e.g., bovine hoof infections, canine otitis, equine wound biofilms), where a multi-pronged strategy could break down the biofilm and kill encased bacteria (Tiwana *et al*., 2025).

Finally, an important gap is the translation of research into policy and practice. There is a need for interdisciplinary efforts involving microbiologists, veterinarians, pharmacologists and regulatory bodies to create pathways for repurposed drugs to be integrated into antimicrobial stewardship programs in veterinary medicine (Vercelli *et al*., 2022). Education of veterinarians about the evidence and proper use of such alternatives will be crucial, as will surveillance to monitor outcomes and ensure that repurposed drug use indeed contributes to reduced conventional antibiotic consumption (Vercelli *et al*., 2022). Economically, incentives or public-private partnerships might be required to fund the necessary trials and to encourage pharmaceutical companies to invest in repurposing off-patent drugs for veterinary markets, which are typically smaller and less lucrative than human markets (Van Boeckel *et al*., 2017). In the context of global AMR, agencies like the OIE (World Organisation for Animal Health) and WHO have advocated for alternatives to antibiotics in agriculture; demonstrating viable repurposed therapeutics could support policies that restrict certain critical antibiotics in animals by providing effective replacements (Vercelli *et al*., 2022; Van Boeckel *et al*., 2017).

In summary, while the foundational science supports the concept of repurposing non-antibiotic drugs as antimicrobials in animals, bridging the gap to real-world application will require addressing questions of efficacy in live animals, appropriate formulation and dosing, safety for animals and consumers and integration into veterinary care protocols (Aggarwal *et al*., 2024; Tiwana *et al*., 2025). Addressing these research gaps in the coming years will be essential for harnessing drug repurposing as a tool to combat AMR in veterinary settings, ultimately contributing to a more sustainable and responsible use of antimicrobials across the One Health spectrum.

CONCLUSIONS

Drug repurposing offers a compelling avenue for expanding the antimicrobial repertoire in veterinary medicine, repurposing existing non-antibiotic drugs to meet the challenges posed by antimicrobial-resistant infections in animals (Aggarwal *et al*., 2024; Tiwana *et al*., 2025). This

systematic review highlights that a wide variety of approved drugs – spanning NSAIDs, antiparasitic agents, anticancer compounds, psychotropics and others – have demonstrated noteworthy antimicrobial or adjuvant effects against veterinary pathogens in recent research (Rajamuthiah*et al*., 2015; Thangamani *et al*., 2015). Through critical analysis of the literature, we found that many of these drugs can directly inhibit bacterial and fungal growth or enhance the efficacy of conventional antibiotics via mechanisms such as membrane disruption, efflux pump inhibition, metabolic interference and immunomodulation (Aggarwal *et al*., 2024; Aloni-Grinstein *et al*., 2025). Notable examples include the use of gallium maltolate in foals as a substitute for antibiotics to treat *R. equi* pneumonia, NSAIDs like celecoxib and diclofenac reducing bacterial load and inflammation in infections, salicylanilide anthelmintics like oxyclozanide exhibiting potent anti-staphylococcal activity and phenothiazine antipsychotics reversing antibiotic resistance by targeting bacterial efflux mechanisms (Cohen *et al*., 2015; Rajamuthiah*et al*., 2015; Thangamani *et al*., 2015). These findings underscore the potential for repurposed drugs to alleviate reliance on traditional antibiotics in animal healthcare, thereby contributing to AMR mitigation efforts (Vercelli *et al*., 2022; Van Boeckel *et al*., 2017).

However, translating these promising leads into clinical practice necessitates further work. Key future steps include conducting rigorous animal trials to validate efficacy and safety, optimizing formulations for veterinary use and establishing guidelines for integrating repurposed drugs into treatment protocols (Aggarwal *et al*., 2024; Tiwana *et al*., 2025). It will also be critical to navigate regulatory approvals, particularly for food-producing animals, to ensure that the use of repurposed drugs does not compromise animal welfare, food safety or public health (Vercelli *et al*., 2022). The interdisciplinary nature of this endeavor is evident – success will require collaboration between researchers, veterinarians, pharmacologists and regulatory agencies to address practical considerations and to monitor outcomes in the field. Importantly, drug repurposing should be viewed as a complementary strategy within a broader antimicrobial stewardship framework in veterinary medicine. By providing alternative or adjunct therapies, repurposed drugs can help preserve the effectiveness of essential antibiotics, reduce the selective pressure for resistance development and ultimately support the health of animals and the protection of human health through reduced zoonotic transmission of resistant bacteria (Vercelli *et al*., 2022; Van Boeckel *et al*., 2017).

In conclusion, the repurposing of non-antibiotic drugs for new antimicrobial uses represents a scientifically sound and potentially impactful approach to innovate within veterinary therapeutics (Aggarwal *et al*., 2024; Tiwana *et al*., 2025). With continued research and careful implementation, this strategy can yield novel treatments for infectious diseases in animals, contributing to improved animal health, enhanced food security and a collective effort to combat the global AMR crisis across the One Health spectrum (Vercelli *et al*., 2022; Aloni-Grinstein *et al*., 2025).

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