Combating Anthelminthic Resistance: A Reappraisal of Management Strategies in Small Animals

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ABSTRACT

Background/Objective- Anthelminthic drug resistance is a serious health threat to dogs and cats worldwide. This problem, which is caused by the widespread and sometimes inappropriate use of anthelmintic drugs, has severely reduced the effectiveness of treatment and has challenged the traditional management of parasitic infections. Therefore, it seems necessary to review and implement new management strategies to combat this phenomenon and maintain the effectiveness of existing drugs.

Method- A comprehensive systematic review of scientific articles published between 2015 and 2024 in reputable databases such as PubMed, Scopus, and Web of Science was conducted. The main keywords used were "anthelmintic resistance", "small animals", "dogs", "cats", and "management strategies". The articles were extracted and analyzed in a structured manner based on predefined screening criteria and data related to resistance mechanisms, diagnostic strategies, and new management protocols.

Results- The results of this systematic review showed that anthelmintic resistance to multiple drug classes, including benzimidazoles, cyclic macrolides, and pyrantel, has been widely reported in roundworm and hookworm populations in dogs and cats. Studies have confirmed the prevalence of resistant genotypes, especially in infections with the hookworm Ancylostoma caninum, which are associated with specific mutations in the genes encoding beta-tubulin and other molecular targets. In addition, nanotechnology has shown significant potential to overcome resistance mechanisms by increasing the bioavailability and targeting of existing drugs. At the same time, initial studies on herbal compounds (phytotherapy) containing secondary metabolites have introduced their synergistic and altruistic effects as promising complementary or alternative options. Furthermore, the results emphasize that single-drug management strategies and subtherapeutic doses have contributed significantly to the selection and expansion of these resistant populations.

Conclusion- Combating anthelminthic resistance requires a paradigm shift towards integrated management. Careful monitoring strategies, smart drug rotation, adherence to hygiene principles, and the use of new technologies such as nanomedicines and complementary herbal compounds should replace reliance solely on periodic treatments.

Keywords: anthelmintic resistance, small animals, management strategies, phytotherapy, nanotechnology

1. INTRODUCTION

Anthelmintic resistance is a global challenge and a growing threat in veterinary medicine, especially in small animals [1, 2]. It occurs when populations of parasitic worms develop resistance to drugs that were previously effective in killing them [3, 4]. The spread of this resistance is largely the result of the widespread, repeated, and sometimes unprincipled use of anthelmintic drugs in animals, which exerts strong selective pressure on the parasites and leads to the survival and proliferation of resistant genotypes [5]. This situation endangers the health and well-being of companion animals and, in addition to increasing the risk of parasitic diseases, is a serious threat to public health, as some of these parasites have the potential to be transmitted to humans [6, 7].

Gastrointestinal parasites, including roundworms (Toxocara spp., Toxascaris leonina), hookworms (Ancylostoma caninum, Uncinaria stenocephala), and whipworms (Trichuris vulpis), are among the most common causes of disease in dogs and cats [8-13]. For decades, control of these infections has been primarily based on the routine and periodic use of anthelmintic drugs in a limited chemical class, particularly benzimidazoles, cyclic macrolides (e.g., ivermectin), and imidazothiazoles (e.g., levamisole) [14]. However, documented and confirmed reports from around the world indicate that the effectiveness of these drugs has decreased significantly due to the emergence and spread of resistance [15, 16]. In particular, multidrug-resistant Ancylostoma caninum has become a serious crisis worldwide, severely limiting treatment options [17, 18].

The mechanisms of resistance are multifactorial and complex, involving genetic changes in parasite populations. These include point mutations in genes encoding drug target proteins (such as the beta-tubulin gene targeted by benzimidazoles), increased activity of drug detoxification and efflux systems, and reduced parasite cuticle permeability [19-21]. The identification of these mechanisms through advanced molecular techniques has deepened our understanding of how resistance develops, but it is also alarming, as it shows that resistance can spread rapidly and even to drugs with similar mechanisms of action (cross-resistance). In the face of this challenge, traditional management approaches based on periodic and uniform deworming of all animals are no longer sufficient and efficient [22, 23]. These approaches have not only failed to slow the progression of resistance but have also indirectly exacerbated the problem by eliminating susceptible parasites and perpetuating resistant populations. Therefore, there is an urgent need to redefine and reappraise management strategies based on epidemiologic principles, continuous surveillance, and judicious use of drugs.

Despite the increasing reports of anthelmintic resistance, there is a lack of coherence and coordination in management strategies to address this problem in small animal clinics. Many veterinarians continue to use outdated protocols due to a lack of access to up-to-date and structured information, which may contribute to the unintended spread of resistance [4, 24]. Furthermore, research on the application of new technologies (such as nanotechnology to enhance drug efficacy (Figure 1)) as well as scientific investigation of herbal compounds as complementary or alternative options is relatively limited [25]. Therefore, a systematic review is needed to collect, evaluate, and synthesize all available evidence on novel management strategies and provide a practical guide for veterinarians. Hence, the main objective of this review is to provide a comprehensive and systematic review of the latest developments and management strategies in addressing anthelmintic resistance in small animals. The potential of nanotechnology and herbal medicines as future strategies will also be explored.

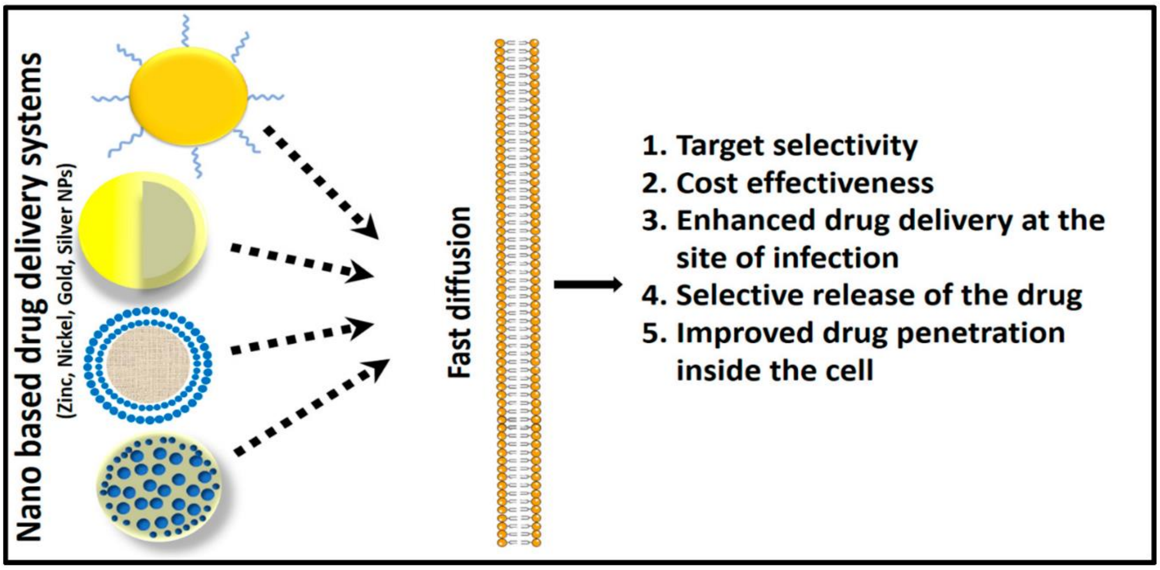

Figure 1. Illustrating various advantages of nano-based drug delivery systems [26] (MDPI Copyright).

2. METHODS AND MATERIALS

A systematic and well-structured methodology was designed and implemented based on the standard PRISMA protocols. A search for relevant articles was conducted in major international scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar, without a time limit until the end of June 2024. The keywords used in the search in English included combinations of the following terms: "anthelmintic resistance" OR "drug resistance" to define the main subject; "small animals" OR "dogs" OR "cats" OR "canine"

OR "feline" to specify the host species; and "management strategies" OR "diagnosis" OR "treatment" OR "control" to identify intervention approaches. To ensure inclusion of emerging solutions, the search was expanded with terms like "nanotechnology" OR "nanoparticles" OR "phytotherapy" OR "herbal medicine" OR "essential oils" OR "plant extracts". Furthermore, to capture data on specific parasitic agents, search terms for major helminths were incorporated, such as "nematode" OR "roundworm" OR "cestode" OR "Toxocara" OR "Toxascaris" OR "hookworm" OR "Ancylostoma" OR "Uncinaria" OR "whipworm" OR "Trichuris" OR "Echinococcus granulosus". Boolean operators (AND, OR) were used to combine and refine the results.

The screening and final selection of articles was carried out in two stages based on predefined criteria (PICOS) and was conducted independently by two reviewers. In the first stage, the titles and abstracts of all retrieved articles were evaluated based on the inclusion criteria (including: studies related to anthelmintic resistance in dogs and cats, original articles, reviews, clinical trials and in vitro/in vivo studies) and exclusion criteria (including: irrelevant articles, articles in a language other than English, studies on large animals, articles without full text available and non-generalizable case reports). In the second stage, the full text of the articles selected from the previous stage was carefully read, and their key data were extracted.

The data extracted from each article were recorded in a standardized form and included information about the author, year of publication, country, type of study, study population (parasite and host), drug class studied, methods for detecting resistance (such as FECRT test, molecular techniques PCR and sequencing), reported resistance mechanisms, proposed management strategies and findings related to new therapies (nanotechnology and herbal). Finally, the qualitative data obtained were categorized, analyzed, and presented in a structured and thematic manner in different sections of the results to comprehensively answer the research questions.

3. RESULTS

The present systematic review paints a worrying picture of the extent and depth of the problem of anthelmintic resistance in small animals, particularly in areas with high animal density. Strong and documented evidence of clinical resistance to the three main classes of anthelmintic drugs - benzimidazoles (e.g., febantel, fenbendazole), cyclic macrolides (e.g., ivermectin, moxidectin), and pyrantel - has been reported in various isolates of nematodes and cestodes of dogs and cats across the world [3, 5, 13, 17, 18, 27-52]. This resistance has been associated in some cases with clinical treatment failure and persistence of clinical signs such as severe anemia and bloody diarrhea in infected dogs.

At the molecular level, several studies have identified the genetic mechanisms underlying this resistance. The strongest and most well-documented evidence is for point mutations in the beta-tubulin gene, which is the main target of benzimidazoles [53]. The mutation at codon 167 (phenylalanine substitution for tyrosine: F167Y) is known to be the strongest predictor of benzimidazole resistance in A. caninum [36, 45, 54-56]. In addition, other mutations at codons 198 and 200 also play a complementary role. In the case of resistance to macrolides, although the mechanism is not completely clear, overexpression of transport proteins of the P-glycoprotein (P-gp) family, which act as efflux pumps and remove drugs from the parasite, is considered a key factor [57, 58]. Advanced next-generation sequencing (NGS) techniques have also revealed the presence of widespread polymorphisms in other candidate genes, increasing our understanding of the genetic complexity of this phenomenon.

From an epidemiological perspective, analyses suggest that the most important driver in the selection and spread of resistant alleles is the frequent and subtherapeutic use of drugs [59]. Periodic and mass deworming programs, carried out without any monitoring or diagnosis, open up a competitive environment for resistant parasites by eliminating susceptible populations and allowing them to multiply explosively [60]. The use of drugs at inadequate doses (e.g., based on incorrect estimates of animal weight) or inappropriate intervals between doses also contributes to this problem. In addition, the continuous contamination of the environment through eggs shed by infected animals that have been ineffectively treated provides a permanent reservoir for reinfections and perpetuates the cycle of resistance.

In contrast, this review has provided strong evidence for the effectiveness of integrated, surveillance-based management strategies. Periodic rotation of drugs with entirely different and non-cross-reactive mechanisms of action (e.g., replacing a benzimidazole with a cyclic macrolide or imidazothiazole derivative) can effectively delay the emergence of resistance before resistance to a drug class is fully established. Combination therapy, which uses two or more drugs with different mechanisms of action, has also been proposed as a promising strategy to eliminate resistant populations and reduce the likelihood of double mutations.

Finally, the findings regarding emerging strategies are very promising. In the field of nanotechnology, it has been shown that the encapsulation of anthelmintic drugs in nanocarriers not only increases their bioavailability and permeability in parasitic tissues but also allows for more precise targeting and controlled drug release, allowing for overcoming efflux mechanisms and thus reducing the required effective dose [61-75]. On the other hand, systematic screening of plant compounds has led to the identification of numerous secondary metabolites (such as terpenes, alkaloids, and flavonoids present in plant essential oils) that have intrinsic antiparasitic activity [76-89].

4. DISCUSSION

The findings of this review clearly confirm that anthelmintic resistance is a future threat and a current and critical reality in small animal medicine that requires an urgent and coordinated response. The prevalence of resistance to multiple drug classes, particularly in Ancylostoma caninum, is a wake-up call that our current drug arsenal is about to lose its effectiveness [33, 35, 90]. By converging the scattered evidence, this study reveals a clear pattern: traditional "one drug fits all" approaches are not only ineffective but also act as a driver of selection for resistant parasites. Therefore, the main debate revolves around the need to shift from a treatment paradigm to an integrated resistance management paradigm, in which treatment is only one link in the chain and not the whole solution. More interestingly, the synergistic effect of herbal compounds with conventional drugs can restore the efficacy of drugs and even target a new point of action in the parasite, which opens a new way to circumvent existing resistances (Figure 2).

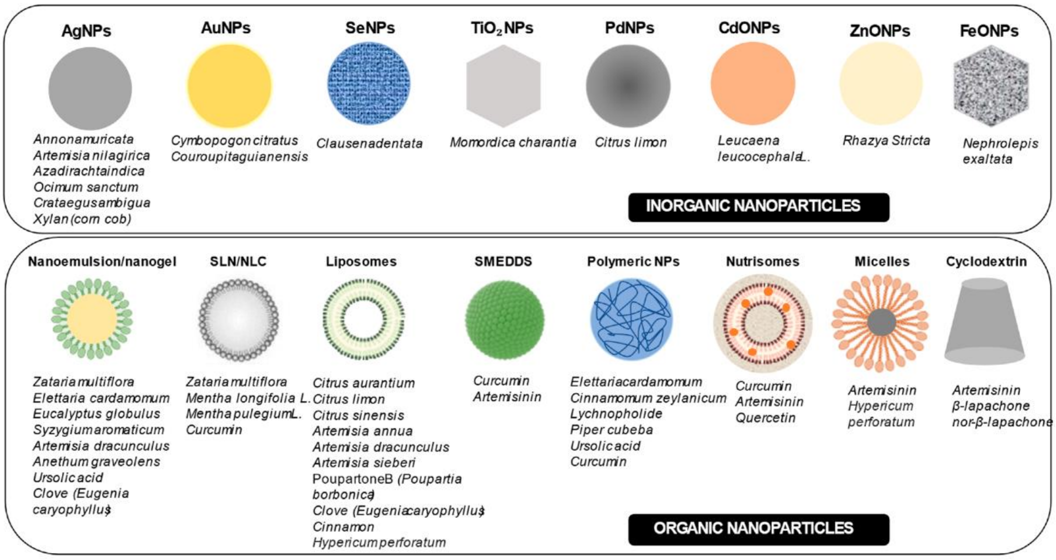

Figure 2. Schematic representation of various inorganic and organic nanocarriers synthesized using plant extracts or phytocompounds for potential application in phytotherapeutic delivery [91] (MDPI Copyright).

Although proposed management strategies, such as drug rotation, have strong scientific support, their implementation in practice faces several challenges. The primary challenge is the limited access to advanced diagnostic tools, such as molecular tests, for general veterinarians, who face the added expense, time consumption, and need for expertise [92]. Moreover, another challenge is the inadequate education of animal owners on the importance of accurate dosing, completion of the course of treatment, and environmental control, which makes their cooperation essential for the success of any management strategy. Furthermore, inadequate monitoring of the over-the-counter sale of anthelmintics in many regions exacerbates these challenges [93, 94].

Looking ahead, research should focus on several key areas. The development of rapid, inexpensive, and accurate point-of-care tests to detect resistance in the veterinary practice is an absolute priority. Moreover, it is essential to invest in the discovery of entirely new drugs with novel molecular targets (such as inhibitors of parasite-specific enzymes) as well as in the optimization of nanoformulations to enhance the efficacy of existing drugs. Furthermore, scientific validation of promising herbal compounds in large-scale clinical trials and standardization of extracts can add valuable options to our toolbox. Finally, the establishment of national and international databases to monitor resistance trends and share data in real time will enable a faster and smarter response to this evolving threat.

Overall, although the challenge ahead is enormous, this review shows that the new strategies and knowledge needed to address it are expanding. The key to success lies in interdisciplinary collaboration between veterinarians, parasitologists, pharmacists, epidemiologists, and animal owners. Adopting a precautionary and prudent approach to the use of anthelmintics, respecting them as a valuable, finite resource, is the most promising way to maintain the effectiveness of these drugs for future generations of animals and to protect public health.

5. CONCLUSION

The conclusion of this study suggests that tackling anthelmintic resistance requires a fundamental paradigm shift from simple periodic treatments to integrated, surveillance-based management. This approach includes the intelligent use of diagnostic tools, implementation of targeted treatment protocols (treatment on demand), strategic drug rotation, careful environmental control, and the use of new technologies (nanotechnology and phytotherapy) as a complement. No single strategy is sufficient; success depends on integrating these strategies into a comprehensive and flexible management plan. Investment in research and development to develop new drugs and tests, alongside extensive training of veterinarians and animal owners, will be the cornerstones of overcoming this global challenge.

Declarations and statements

Funding

No funding was received to conduct this study.

Conflict of interest

The authors declare that they have no conflict of interest.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval

All applicable international, national, and/or institutional guidelines for writing a review paper were followed.

Author contribution

Conceptualization: [Marzieh Saki], …; Methodology: [All Authors], …; Formal analysis and investigation: [All Authors], …; Writing - original draft preparation: [All Authors]; Writing - review and editing: [Sina Rouzmehr], …; Funding acquisition: [Self-funding], …; Supervision: [Marzieh Saki].

Consent to participate

Not applicable

Consent for publication

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Declaration of the use of generative AI

This paper was composed without the use of any artificial intelligence tools for any aspect of its creation.

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