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บทความวิจัย

# ภาวะการดื้อยาและทางเลือกในการป้องกันเห็บในปัจจุบัน

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**คำสำคัญ**

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เห็บเป็นปัญหาสำคัญในสัตว์เลี้ยงและปศุสัตว์ เนื่องจากมีบทบาทสำคัญในการถ่ายทอดโรคและส่งผลกระทบต่อสุขภาพทั้งในมนุษย์และสัตว์ การศึกษานี้มีวัตถุประสงค์เพื่อศึกษากลไกการดื้อยาสำหรับเห็บ การศึกษากลุ่มยาฆ่าแมลงชนิดใหม่สำหรับการป้องกันและควบคุมจำนวนเห็บ ที่เป็นประโยชน์ต่อสุขภาพของมนุษย์และสัตว์ และสำรวจแนวโน้มที่เกิดขึ้นใหม่ของผลิตภัณฑ์ที่เป็นมิตรต่อสิ่งแวดล้อมในการกำจัดเห็บ ในปัจจุบันมีการพัฒนาผลิตภัณฑ์และคิดค้นวิธีการใหม่เพื่อควบคุมประชากรเห็บที่มีประสิทธิภาพในการจัดการปัญหานี้ อย่างไรก็ตาม ได้พบว่าประสิทธิภาพเหล่านี้ลดลงในช่วงไม่กี่ปีที่ผ่านมา ซึ่งเป็นผลมาจากการกลายพันธุ์หรือส่งต่อของยีนดื้อยาของเห็บ ปัญหาการดื้อยาในเห็บส่งผลกระทบต่อทั้งทางการแพทย์และสัตวแพทย์ และทวีความรุนแรงขึ้นอย่างต่อเนื่อง โดยมีสาเหตุมาจากการใช้ยามากเกินความจำเป็น การใช้ยากลุ่มสารเคมีต่างๆ ที่มีการใช้มาเป็นเวลานาน นอกจากจะมีประสิทธิภาพที่ต่ำลง สิ่งหนึ่งที่ไม่ควรมองข้ามคือการปนเปื้อนของกลุ่มยาและสารเคมีในสิ่งแวดล้อม ในปัจจุบันจึงได้มีการให้ความสำคัญในการใช้วิธีการกำจัดเห็บที่เป็นมิตรต่อสิ่งแวดล้อม เช่น สารสกัดจากสมุนไพร ไปจนถึงวิธีการทางภูมิคุ้มกันและการป้องกันด้วยวิธีชีวภาพต่าง ๆ การศึกษาและวิจัยแนวทางในการกำจัดเห็บทางเลือกใหม่จึงน่าสนใจเป็นอย่างมาก การดื้อยาของเห็บนี้อาจมีสาเหตุมาจากการใช้ยาที่มากเกินความจำเป็นหรือใช้ยาไม่ถูกต้อง จึงควรมีการทำความเข้าใจกลไกการเกิดการดื้อยาด้วย

## Introduction

The problem of drug resistance is significant for the veterinary and medical fields and can be the cause of the barrier to effective tick prevention. One reason is the misuse and lack of knowledge in appropriate procedure for chemical application (Eisen & Stafford, 2021). Discriminatory drug use contributes to the worsening of this issue. Elevate the dosage or switch to a different medication if greater efficacy was required. Both the patient and the surroundings suffer as a result of this. Nowadays, people are concerned about resistance, negative side effects, and persistent effects.

Drug resistance arises due to genetic mutations, a capability inherent in all organisms, including parasites. Especially ticks, the important parasites in livestock and pets, which have different species. The common species are *Rhipicephalus* (*Boophilus*) *microplus* (*R. microplus*) in cattle and *Rhipicephalus sanguineus* (*R. sanguineus*) in dogs. There are many reports about the insecticides and acaricides resistance in ticks from all over the world as Asia, America, Africa and also in Australia were reported (Abbas et al., 2014). Due to this cause, the situation of tick prevention has grown worse. The new insecticides and acaricide products were developed to solve this problem. Whereas chemical products leave the residue in the environment and their toxicity can affect both humans and animals. The alternative ways are environmental control, biological control, immunological control, and herb products, which are recommended for use. The aim of

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this study is to clearly understand the mechanism of drug resistance in ticks and review new insecticides and acaricides product for tick prevention and kill which affect to human and animal health and probably a new trend to be an environmentally friendly product.

*The importance of drug resistance in ticks*

The drug resistance was reported from all areas of the world. The resistance of the cattle tick to ivermectin was first detected more than 20 years ago in Brazil; moreover, fipronil (phenylpyrazolic insecticide) was also first reported in Brazil, using in vitro larval bioassays to diagnose (Martins & Furlong, 2001; Castro-Janer et al., 2011).

It was discovered that amitraz, BHC/cyclodienes, and organophosphates caused resistance in *R. sanguineus*. Ticks that infest dogs and cats have not had their acaricide resistance as thoroughly examined as cow ticks, particularly *R. microplus*, which has been intensively studied due to its economic significance to the cattle industry and its resistance to numerous compounds.

Multi-acaricide resistant ticks have resulted in an unprecedented incidence of acaricide failure in central and western Uganda, according to research conducted in 2018 by Vudriko and colleagues. Additionally, a different in vitro study conducted in 2016 was the first to document the establishment of multi-acaricide- and super synthetic pyrethroid-resistant Rhipicephalus ticks in Uganda. (Vudriko et al., 2016; Vudriko et al., 2018).

Rodríguez-Vivas et al. (2014) reported *R. microplus* resistance to ivermectin and acaricides in Mexican cattle farms. In the Mexican veterinary market, macrocyclic lactones are the most often used antiparasitic medication. There have been reports of *R. microplus* populations resistant to ivermectin in Brazil, Uruguay, and particularly Mexico. While the majority of *R. microplus* from Mexico had modest levels of ivermectin resistance, certain field populations of the species showed significant levels of ivermectin resistance. Many *R. microplus* field populations are resistant to many antiparasitic medication classes, such as phenylpyrazole pyrethroids, amitraz, ivermectin, and organophosphates (Rodríguez-Vivas et al., 2014; Shakya et al., 2020; Torrents et al., 2020).

On the other hand, Coles and Drydens were reviewed and found that the use of insecticide/acaricide not effective in fleas and ticks infesting dogs and cats most likely cause of lack of the efficacy in these drugs rather than the resistance (Coles & Dryden, 2014). The research conducted by Lavan and colleagues investigated the behavior of pet owners regarding tick and flea control in the United States. Their findings revealed a decrease in the recommended period for flea and tick protection as indicated by veterinary guidance. (10.6 months per year). Veterinarians adhere to the guidance of the Companion Animal Parasite Council (CAPC) by endorsing a 12-month regimen for flea and tick prevention (Lavan et al., 2017).

*What is resistance?*

Although the official definition of resistance is a change in the target species of susceptibility to a treatment, resistance is typically first identified as a drug's inability to suppress parasitism. "The ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject" is the broad definition of resistance developed in 1965 by the Scientific Group of the World Health Organization. Discussions on acaricide resistance could be started with such a general term.

*Type of resistance*

Three categories of resistance were added to the definition of pesticide resistance by the WHO in 2012, as noted by Coles and Dryden (Coles & Dryden, 2014). It is notable that the WHO formerly used to categorize the different types of resistance. Gene and molecular-level methodologies are employed for identification purposes. Furthermore, the analysis encompasses the assessment of outcomes influenced by drug resistance.

Molecular genotyping of resistance

The identification of the genes causing an inherited resistance trait provides proof of the evolutionary process by molecular genotyping of resistance.

Phenotypic resistance

This approach assesses susceptibility to a standard dose by using the 1957 definition of resistance, which is "the development of an ability, in a strain of insects, to tolerate doses of toxicants that would prove lethal to the majority of individuals in a normal population of the same species."

Resistance resulting in control failure

The WHO was mainly concerned with malaria, which is defined as an insecticide's inability to prevent the spread of illness via an insect vector. This "control failure" could be interpreted as an inability to manage flea-induced dermatitis or any of the other illnesses spread by fleas and ticks.

Whereas, Abbas and co-workers divided the type of resistance into three types: identity by inheritance result in Table 1 (Abbas et al., 2014).

**Table 1** Inheritance patterns of resistance into three types

| Inheritance Pattern | Characteristics |
|---|---|
| Acquired resistance | Resistance that results from heredity, which leads to decreases in sensitivity to drugs with the passage of time The drug's concentration and the level of resistance are directly correlated. When a medication is given at a reduced concentration, a strain that was under control with a single dose of the treatment may develop resistance. |
| Cross-resistance | The sharing of resistance across several acaricides that function in a comparable way. |
| Multiple resistance | Tolerance to many medications, notwithstanding their distinct mechanisms of action. |

*The mechanisms of resistance*

Genetic alterations, commonly manifesting within the population, are the primary contributors to resistance against antiparasitic drugs. When a class of drugs is first developed to treat parasites, resistant alleles are rare; but, as treatments become more popular, selection pressure on the resistant alleles increases, and the number of resistant individuals increases (Wolstenholme & Martin, 2014). It has been noted that all of the parasites mentioned above are resistant to many medication classes (Table 1). The mechanisms of resistance to all medications in a class are often the same. Acetylcholine (ACh) is an organic compound released by arthropod nerves into the intracellular space (synapse) where the nerve cell contacts a muscle cell or another nerve cell. Acetylcholine stimulates the muscle cell to contract, and contraction is stopped by acetylcholinesterase (AChE) that destroys the released ACh signal molecules. Acetylcholinesterase is blocked by organophosphates like malathion and diazinon, which causes paralysis in the target arthropod species. In summary, the acute toxicity of organophosphates arises from their chemical binding to the acetylcholinesterase (AChE) enzyme, thereby inhibiting its ability to break down acetylcholine (ACh). As a result, the arthropod dies with its nervous system and muscles in a prolonged state of excitation and contraction (Horsak et al., 1964). In parasites, resistance to organophosphates can arise from two different mechanisms. Firstly, resistance to malathion is linked to an upregulation of esterase and cytochrome P450 enzyme expression, which can metabolize the drug before it affects the intended target species. The other method of resistance to organophosphates involves upregulating AChE transcription to offset its (McNair, 2015).

**Table 2** Mechanism of action and Resistance in ticks

| Acaricides | Target | Mechanism of action and resistance | References |
|---|---|---|---|
| Organophosphates | Acetylcholinesterase | Resistance to organophosphates in tick can | Kumar (2019) |

| | | | |
|---|---|---|---|
| | | be attributed to modifications in the Acetylcholinesterase gene, carboxylesterase gene, and metabolic detoxification. | |
| | | Overexpression of esterases in larvae and adult tick can lead to resistance. | Villarino et al. (2001) |
| | | Changes in metabolic activities, conformational changes in acetylcholinesterase. | Pruett (2002) |
| Formamidines (Amitraz) | Octopamine tyramine | Amitraz resistance is a complex multigenic trait with recessive alleles. | Li et al. (2004) |
| | | Nucleotide mutations in the octopamine tyramine receptor gene in Rhipicephalus ticks are linked to resistance, causing target insensitivity. | Baron et al. (2015) |
| Synthetic Pyrethroids | Voltage-gated sodium channel | Synthetic pyrethroids resistance is linked to mutations in voltage-gated sodium channel genes. | Morgan et al. (2009) |
| Macrocyclic lactones | Glu-Cl channel | Ticks are resistant to MLs, and mutations were observed in the Glu-Cl gene of R. microplus ticks | Aguilar-Tipacamú et al. (2016) |
| Fipronil | GABA-gated chloride channel | Tick resistant to fipronil showed mutations in the second and third transmembrane domains of the GABA-gated chloride channel gene. | Janer et al. (2019); Janer et al.. (2021) |

*The alternative ways to control ticks*

One of the alternative medical choice and regimen for ectoparasite management is the resistance of tick control treatments. Other significant factors include the existence of medication residues and related negative effects. According to Turner's 2011 survey, between April 2007 and May 2009, 708 companion animal incident reports involving spot-on flea and tick control chemical products were received by Health Canada's Pest Management Regulatory Agency (PMRA), which oversees pesticide use in the country. There were 42 cats and 1 dog reported dead. These elements drive the quest for an innovative tick management strategy that is safer and more effective for customers, owners, animals, and the environment (Turner et al., 2011).

*1. Environmental management control*

This is a highly effective method for preventing tick infestations, particularly within pastures where cows graze and consume vegetation. For this reason, ticks prefer to live in pastures where they can lay their eggs and wait for their next meal. The standard environmental management strategy that Abbas recommended in 2014 (Abbas et al., 2014) such as:

*1.1 Pasture Burning*

In various countries, such as South Africa, Australia, Zambia, and the United States of America, the practice of burning pasture during the dry season (winter) induces a "green flush," contributing to the effective control of tick populations. The crack areas can be the egg laying sites for ticks. Since ticks have a tendency to recolonize burned areas, burning pastures is a technique used to control all tick stages (Rahman et al., 2022). However, because of worries about air pollution, frequent pasture burning may be difficult for cattle farmers in poorer nations.

*1.2 Pasture alternation and/or rotation*

Keeping grazing areas free of cattle until the larvae die is another method of managing pastures. This method, when paired with chemical acaricide sprays, has been shown to be an efficient means of controlling cow ticks. The most practically priced way to lower tick populations was to rotate pastures and use acaricides or convert existing habitats.

*1.3 House management*

Due to the larvae's enhanced capacity to locate hosts, there are increased opportunities for tick infection rates in tropical and semitropical regions. Creating an environment that is inhospitable to the free-living stages of the tick may help lower the likelihood of tick infestations in feedlot cattle. The management of cattle in feedlots involves several key variables, including optimal animal density, minimal stress, regular and thorough cleaning, good ventilation, and effective management of feed and water.

*2. Chemical control*

Despite several challenges, such as the emergence of resistance, public apprehension regarding food residues, and environmental degradation, this method remains the most extensively employed worldwide. Of all these synthetic pyrethroids, macrocyclic lactones particularly ivermectin, which is widely used in Thailand even as an extra-label drug have been shown to have superior residual activity against a wide range of insect species and efficiency at lower dose rates. However, ivermectin's ability to eradicate ticks is no longer reliable. Previously used to effectively control ticks, macrocyclic lactones impede the transmission of electrical activity in nerves and muscle cells by increasing the release and binding of gamma-aminobutyric acid (GABA) at nerve endings. Although *R. microplus* has shown partial resistance as a result of heavy use, the precise mechanism of resistance in ticks and parasitic mites is yet unknown (Lovis et al., 2013; Martins & Furlong, 2001; Perez-Cogollo et al., 2010). The current study offered a comprehensive evaluation and enhancement of the most widely used techniques for identifying acaricide resistance in order to identify ivermectin resistance. Additionally, this study presents a straightforward, precise, and dependable in vitro method for identifying ivermectin resistance in *R. microplus*. These tests were put into practice and used to track resistance in the Brazilian state of São Paulo, and the results showed that resistance is common. Moreover, it causes an intolerable amount of chemical residue in food supplies like meat and meat products, which are harmful to humans.

Fluralaner is one of the isoxazoline classes of antiparasitic drugs that represent safe and effective new acaricidal and insecticidal products for dogs to control ectoparasitic infestations. Extensive evidence supports its robust efficacy against ectoparasites, coupled with its demonstrated safety when administered orally (Chiummo et al., 2023). This new chemical product for tick prevention in dogs is really interesting these days in Thailand. Fluralaner is a very strong arthropod-specific GABA-gated chloride channel inhibitor, according to in vitro testing. It also has a less strong but still noticeable inhibitory effect on arthropod glutamate-gated chloride channels, and its receptor binding on arthropod GABA-gated chloride channels is 5–236 times better than fipronil. Because of this difference in receptor potency, fluralaner may be more effective than fipronil in controlling ectoparasites in the field (Rohdich et al., 2014).

*3. Biological control*

Biological control emerges as an environmentally sustainable alternative to the utilization of pesticides and acaricides. Arthropod control has been studied using a variety of biological control methods, such as the application of fungi and essential oils. Utilizing peptides derived from spider venom represents a recently developed biological control strategy for arthropod parasites. Arachnids possess a diverse repertoire of venom peptides, many of which exhibit neurotoxic properties in other arthropods. These peptides specifically target sodium and calcium channels in arthropod neurons, inducing paralysis. The topic is still in its early phases of research, and considerable work has to be done to determine which peptides should target which spectrum of arthropods. In addition, the peptides must not be harmful to humans or any other host species. The mode of delivery must also be taken into account, since the majority of in vitro experiments entail injecting venom peptides directly into the arthropod. To determine the most efficient method of administering these bio-insecticides, more research in this area is necessary (Windley et al., 2012).Entomopathogenic fungi are fungal species which can harm arthropods (Rajula et al., 2020). The most studied entomopathogenic fungus for against *Rhipicephalus microplus* ticks in the laboratory and the field are *Metarhizium anisopliae* sensu lato (s.l.) and *Beauveria bassiana* s.l. (Alonso-Díaz & Fernández-Salas, 2021). Moreover, under field conditions, the effectiveness of the entomopathogenic fungus *Metarhizium brunneum* in suppressing the tick *Rhipicephalus annulatus* was investigated. The amount of tick eggs was affected by this fungus, which decreased the percentage of female ticks laying full-size egg masses and decreased the hatchability of the eggs (Samish et al., 2014). Additionally, Fischhoff and colleagues investigated the effectiveness of *M. brunneum* (*M. anisopliae*) strain F52, an entomopathogenic fungus, as a tick biocontrol agent in lowering the number of Ixodes scapularis. The goal of the research is to verify that this fungus has no effect on other non-target arthropods (Fischhoff et al., 2017).

*4. Immunological control*

While not universally applicable to all tick species, the development of a protective vaccine emerges as a prospective alternative control strategy for specific arthropod infections in various areas and alsoconsidered as one of the best alternative approaches to control ticks and tick-borne diseases (Abbas et al., 2023; Rahman et al., 2022). The only tick species that has been researched in Thailand is *R. microplus*. It would not be strategically feasible to vaccinate every individual at risk of infestation for every disease. It is a viable substitute for many veterinary parasites, nevertheless.

The vaccination is founded upon the *R. microplus* rBm95 gut antigen. This immunization approach aims to disrupt the cell wall of the tick's gastrointestinal tract. Consequently, as these ticks are rendered incapable of converting blood into eggs, there is potential for a reduction in tick populations. Additionally, vaccination prevents the toxicity of the tick's mouth portion (Jittapalapong et al., 2010). The vaccination makes tick management practical, economical, and most importantly, environmentally friendly, significantly lowering the demand for acaricides. Field research conducted in Brazil on the multi-antigenic vaccine targeting the cow tick *R. microplus* showcased its superior efficacy in comparison to the control group (Parizi et al., 2012). Further research on the humoral immune response of dairy calves inoculated with rBm95 (KU-VAC1), a protein produced from Thai *R. microplus*, is available. The study's findings showed that KU-VAC1 and Gavac are equally immunogenic, and that more research is necessary to examine the effectiveness of ticks fed to cattle who have received vaccinations (Jittapalapong et al., 2010).

*5. Herbal extract control*

An emerging trend in the veterinary sector involves the utilization of botanicals on livestock for tick control. More than 100 plant species were studied for their acaricidal and repellent effect on ticks. Most are plants in Lamiaceae family (Nwanade et al., 2020). The following analysis of reports makes it evident that a variety of botanical products are effective at killing ticks or preventing their oviposition (Abbas et al., 2014).

The herb that Thai people are familiar with that has acaricidal properties, such as *Stemona collinsae* (Jansawan et al., 1993), *Ocimum suave* (Mwangi et al., 1995), peel oil of *Citrus* spp. (Chungsamarnyart & Jansawan, 1996), *Gynandropsis gynandra* (Lwande et al., 1999), *Tamarindus indicus*

(Chungsamarnyart & Jansawan, 2001), *Eucalyptus* spp. (Chagas et al., 2002), *Senna italica* subsp. *arachoides* (Magano et al., 2008) *Annona squamosal* leaves (Madhumitha et al., 2012) and neem (Giglioti et al., 2011). A natural substance called Azadirachtin is obtained from the neem tree (*Azadirachta indica*). The maximum concentration of azadirachtin, which can reach 40 % in the extracted oil, is found in the fruits of this plant. It has been demonstrated that azadirachtin inhibits vitellogenin during arthropod oogenesis. Since then, it has been observed to inhibit growth and discourage feeding in a variety of arthropod species. It has demonstrated efficacy as an insecticide against a range of agricultural pests. Although azadirachtin has been studied as an acaricide against ticks and poultry mites, where it was able to kill 90 % of mites in vitro, research on it as a control agent for medical and veterinary arthropods has been more restricted. Since azadirachtin is present in many commercial preparations of neem oil and is safe to people, it presents a viable substitute for the pesticides currently used to control arthropod infestations (Giglioti et al., 2011).

## Conclusion

Drug resistance in ticks is a prominent issue highlighted in the veterinary field, exerting potential implications on human health. The main cause due to discriminating drug use leads to accelerating this problem getting worse. Although the drug resistance developing is an ability of all organism to survive and transfer to next generation more tolerate doses of acaricide/insecticide products. Nevertheless, responsive drug use can slow down this problem.

Moreover, the contemporary shift towards eco-friendly approaches is noteworthy. Biological and immunological controls, along with herbal extracts, represent alternative methodologies for mitigating the impact of ticks, significant vectors in this context. Research on methods for eliminating and preventing ticks is in its early stages, and further study is considered necessary.

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Research article

# An updated review of drug resistance in ticks and the alternative ways for tick prevention

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ABSTRACT

Ticks, as significant vectors for various diseases in both companion and livestock animals, pose a threat to animal health and can also impact human well-being. This study aims to explore the mechanism of tick drug resistance, examine novel insecticides and acaricides for tick prevention and control, with potential benefits for human and animal health, and explore the emerging trend of environmentally friendly products. Recently, efforts have been made to develop products and procedures to control tick populations, yielding effective results for a considerable period. However, the efficacy of previously successful products has diminished in recent times. This decline in effectiveness is primarily attributed to genetic mutations causing drug resistance. The issue of drug resistance in ticks has significantly impacted both the medical and veterinary sectors and is escalating steadily. The exacerbation of this problem is primarily driven by the indiscriminate use of drugs. It is crucial not to overlook the concern of chemical residues. Currently, there is a growing emphasis on environmentally friendly approaches to tick management, such as herbal extract products, as well as exploring immunological and biological methods. Further research into these alternatives holds considerable interest. This resistance can result from overuse or misuse of these chemicals. Understanding the mechanisms of resistance and developing alternative strategies is crucial.

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