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Review article

Drug resistance in blood parasitic infections in cattle: a review

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ABSTRACT. Generally the most common blood parasites identified in cattle are protozoa in the genera *Trypanosoma*, *Theileria*, *Babesia*, and rickettsia in the genus *Anaplasma*. These parasites can cause clinical symptoms and productivity loss which will therefore consequently in economic loss. At present, blood parasite infection in cattle often has poor treatment outcomes and there is an increase of reports which indicating that drug resistance may occur in treating infections. *Trypanosoma vivax*, *T. congolense*, and *T. brucei* have been reported for resistance to isometamidium chloride and diminazene aceturate drug. *Babesia bovis* is resistant to diminazene aceturate drug, and *Anaplasma marginale* and *A. centrale* are resistant to oxytetracycline drug. The most common methods for diagnosing drug resistance are block treatment, *in vivo* standardized drug sensitivity tests, and molecular tools. Drug-resistant causes a decrease in treatment performance, therefore, new methods have been developed for choosing appropriate treatment of blood parasitic infection including using a primary drug combined with other substance, using herbal extracts, or developing a new effective drug.

Keywords: blood parasites, drug resistance, cattle

Introduction

Blood parasitic diseases in livestock consist of trypanosomosis, theileriosis, babesiosis, and anaplasmosis [1]. *Trypanosoma congolense*, *T. vivax*, *T. brucei*, and *T. evansi* are the unicellular flagellated protozoans which cause trypanosomosis in cattle [2]. The morphology of trypanosome parasites varies between species and differentially depends on stages of infection, however, the trypomastigote form is the flagellated stage found in the peripheral bloodstream and used for routine diagnosis [2–4]. Moreover, trypomastigote of *T. evansi* is similar to *T. brucei* and cannot be identfied with morphology classification [2,4]. Some studies also classify *T. evansi* as a subtype of *T. brucei* [4]. The clinical manifestations of trypanosomosis include anemia, fever, decreased milk in dairy cows, edema, and death may occur in severe or chronic infection [5]. For the treatment of trypanosomosis in cattle dosages of diminazene aceturate at 3.5 mg/kg, homidium bromide at 1 mg/kg, homidium chloride at 1 mg/kg, isometamidium chloride at 0.25–1 mg/kg and quinapyramine sulphate at 3–5 mg/kg, are respectively registered [3].

Babesia is a protozoan infecting erythrocytes or piroplasm and transmitted with ixodid ticks. Four species belonging to the genus *Babesia* responsible for most frequent infections in cattle are *B. bovis*, *B. bigemina*, *B. divergens* and *B. major*. *Babesia bovis* and *B. divergens* are classified into the group of small *Babesia* (1.0–2.5 μm), however, *B. bigemina* and *B. major* belongs to large *Babesia* group (2.5–5.0 μm) [2,6]. Clinical signs of babesiosis consist of high fever, loss of appetite, decreasing milk production, weakness, hemoglobinuria and jaundice [5]. Nevertheless, the clinical signs depend on many factors such as strain of parasites, host immune response and co-infection with other blood parasites. In addition, older animals are more susceptible to parasitic infection and exhibit more severe symptoms. Drug treatment for babesiosis in cattle are imidocarb with 1–3 mg/kg and diminazene aceturate with 3–5 mg/kg [7].

Anaplasmosis is resulted from red blood cell infection with rickettsia in the genus *Anaplasma.* The

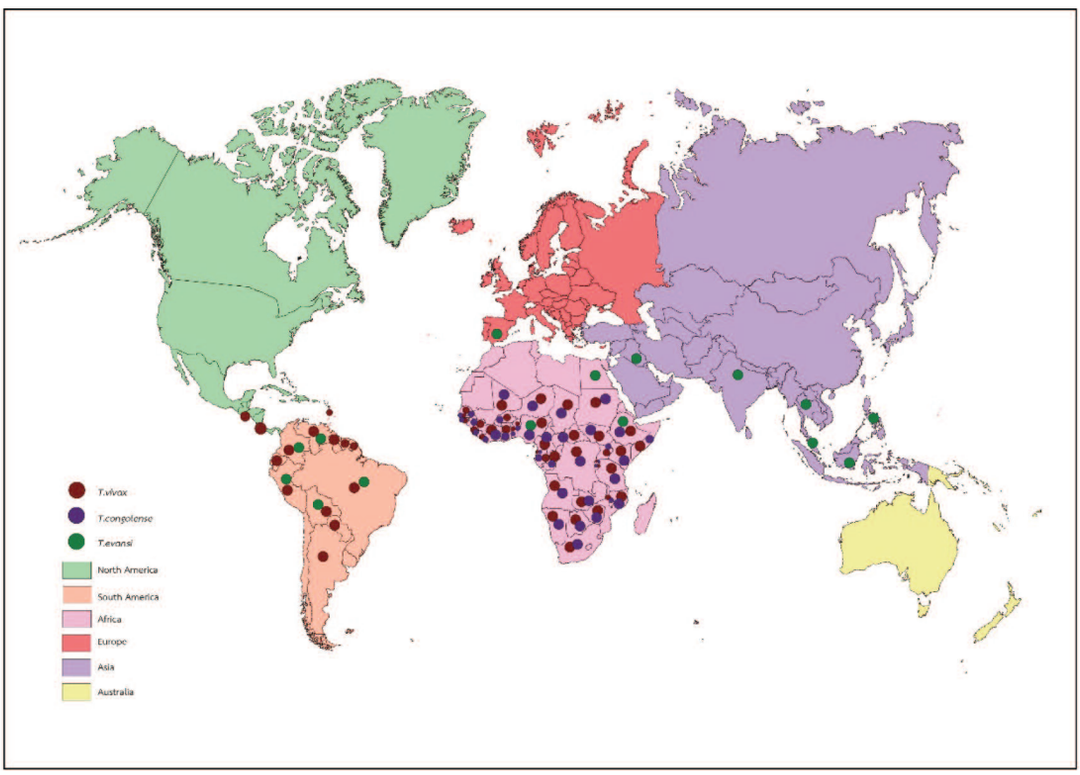

Figure 1. Geographic distribution of *T. evansi*, *T. congolense* and *T. vivax* infection in cattle

three species found most often in cattle are *A. marginale*, *A. centrale* and *A. caudatum*. In anaplasmosis, clinical symptoms comprise of fever, anorexia, lethargy, atonic rumen, constipation, dark brown feces containing mucous and anemia [5]. However, infections with *A. centrale* and *A. caudatum* are less severe compared with *A. marginale*. Drugs of choice for treatment are tetracyclines group such as tetracycline, chlortetracycline and oxytetracycline [2] with 20 mg/kg [8].

These blood parasitic diseases have a significant impact on animal health and productivity. The management strategies for timely in diagnosis, prevention and treatment of diseases should be improved to make the more effectively. Interestingly, increasing drug resistance from these parasites has occurred and lead to reduction in the effectiveness of parasite therapy [9]. The appearance of incurable diseases, heavy productivity loss and consequently heavy in economic loss [10]. The information of this review will enable us to better understand the situation of drug resistance in blood parasitic infections in cattle and new approaches for the treatment of blood parasites. Understanding the situation of drug resistance in cattle is necessary for developing and achieving programs to control blood parasitic diseases in cattle. The information of drug resistant is research needed for understanding the transmission, distribution and control of these blood parasite diseases.

Epidemiology of *Trypanosoma*

For life cycle, *Trypanosoma* necessitates two hosts to complete. Vertebrate hosts are required more than one species including camel, cattle, horse and dogs and invertebrate hosts are horse flies [11]. *Trypanosoma evansi* has been reported in cattle from 1909 to 2017 in Africa, Asia, South America and Europe. In Africa, *T. evansi* infection is reported in Egypt, Ethiopia and Nigeria with infection rates range from 6–42% [12]. In Asia, prevalence of *T. evansi* infection reported in India, Indonesia, Iraq, Malaysia, Philippines, and Thailand varies between 1–61% [12]. In South American, prevalence of *T. evansi* infection in cattle was 3–40% in Bolivia, Brazil, Colombia, Peru and Venezuela. The differences in the infection rates may be explained due to the sensitivity of diagnosis techniques (parasitological methods, antibody-based detection methods and molecular method). In Europe, it has been reported only in Spain with 5% infection rate established by antibody-based detection methods [12] as shown in figure 1.

The life cycle of *Trypanosoma vivax* also

involves vertebrate and invertebrate hosts. The vertebrate hosts include cattle, goats, sheep, horses, and camels. The vector hosts are tsetse flies (*Glossina* spp.) [13]. *T. vivax* endemics in Africa, South America and North America with a prevalence of approximately 6.4% [14]. In South America, infections have been found in Guyana, Argentina, Venezuela, Colombia, Ecuador, Peru, Bolivia, Paraguay, Brazil, French Guiana and Suriname. In North America, infection can be found in Costa Rica, El Salvador, and Martinique. In Africa, *T. vivax* reported in 38 of 54 countries where consist of Mali, Senegal, Gambia, Guinea-Bissau, Guinea, Sierra Leone, Liberia, Cote D'Ivoire, Ghana, Togo, Benin, Burkina Faso, Nigeria, Niger, Chad, Cameroon, Central African Republic, Sudan, South Sudan, Ethiopia, Somalia, Kenya, Uganda, Democratic Republic of Congo, Congo, Gabon, Equatorial Guinea, Rwanda, Burundi, Tanzania, Mozambique, Malawi, Zambia, Angola, Namibia, Botswana, Zimbabwe and South Africa [15,16].

For *T. congolense*, the infection has been reported only in Africa [16]. The vector hosts are tsetse flies (*Glossina* spp.). The geographic distribution of *T. evansi*, *T. congolense* and *T. vivax* in cattle demonstrated in figure 1.

Drug resistance mechanism

In general, the mechanism of drug resistance in *Trypanosoma* is primarily due to reduction of drug uptake and increase drug of export by resistant cells [17]. The principal causes of the isometamidium chloride resistance process arise from (a) decreasing in diffusion through the mitochondrial membrane of the organism, (b) changes in the transporter located in the inner mitochondrial membrane and (c) increasing the extrusion of the drug from the transporter in the cytoplasm membrane. However, all three processes may occur together and promote the process of severe drug resistance [18].

Trypanosoma diminazene aceturate resistance has been associated with the loss of transporter function of the P2-type purine transporter which contributes to the uptake of diminazene aceturate drugs into the parasite cell. Functional loss of the P2-type purine transporter is due to the lack of or non-expression of the P2-type purine transporter *Tb*AT1 gene in *T. brucei, Tco*AT1 gene in *T. congolense* and *Te*DR40 gene in *T. evansi* which might be a factor contributing to high diminazene aceturate resistance [18,19].

Situation of blood parasitic resistance in cattle

Bovine *Trypanosoma* parasite resistance to blood parasitic drugs reported for more than 50 years [20,21]. The types of blood parasitic drugs and *Trypanosoma* species that were recorded to be resistant are varied due to each area having outbreaks of different types of *Trypanosoma*, and

Table 1. Situation of blood parasitic drug resistance in cattle in the past 10 years

Continents	Countries	Drugs	Analysis methods	Parasites	Reference
Africa	Burkina Faso	isometamidium chloride, diminazene aceturate	block treatment	*T. vivax*	[27]
	Mali	isometamidium chloride, diminazene aceturate	block treatment	*T. vivax*, *T. congolense*	[28]
	Ethiopia	isometamidium chloride, diminazene aceturate	block treatment, molecular tools	*T. vivax*, *T. congolense*, *T. brucei*	[10,22,23]
	Togo	isometamidium chloride, diminazene aceturate	block treatment, molecular tools	*T. congolense*	[29]
	Cameroon	isometamidium chloride, diminazene aceturate	molecular tools	*T. congolense*, *T. brucei*	[30]
Asia	Japan	diminazene aceturate	*in vitro* test	*B. bovis*	[9]
	Iran	oxytetracycline	molecular tools	*A. marginale*, *A. centrale*	[33]

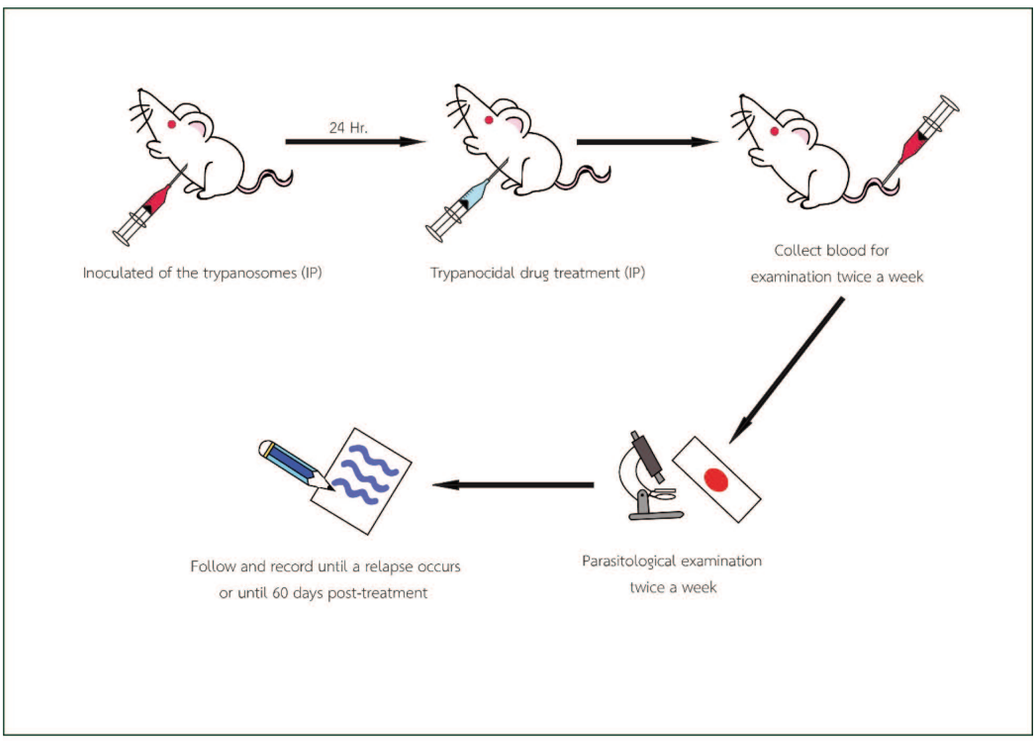

Figure 2. *In vivo* standardized drug sensitivity tests on isolated field-strains in mice

the different drugs available in different areas [22,23]. Trypanosomosis resistance in Africa may be more prevalent. More than twenty out of 54 countries have reported resistance to blood parasitic drugs included Burkina Faso, Cote D'Ivoire, Chad, Ethiopia, Kenya, Nigeria, Somalia, Sudan, Tanzania, Uganda, Zimbabwe, Central African Republic, Zambia, Cameroon, Mozambique, Benin, Ghana and Togo [18,24]. In South America, *T. vivax* resistant to diminazene aceturate was found in cattle in French Guiana [25]. In Asia, *T. evansi* resistance to suramin and antrycide was reported in China [26]. However, in Europe and Australia, there has been no reports of drug resistance to *Trypanosoma* parasite infection in cattle.

Drug resistance in *Trypanosoma* parasite has been reported in cattle over the past 10 years (2011–2020) but only in Africa, and not on any other continent. *Trypanosoma vivax*, *T. congolense* and *T. brucei* resistant to diminazene aceturate and isometamidium chloride were reported in Burkina Faso, Mali, Ethiopia, Togo, and Cameroon (Tab. 1). The methods used to detect resistance were block treatment [10,23,27–29] and molecular tools [22,29,30]. Interestingly, trypanosomiasis resistance to the isometamidium chloride was greater than to diminazene aceturate [23,28,29]. However, another study reported different results that *Trypanosoma* infected cattle are more resistant to diminazene aceturate than to isometamidium chloride [30].

Additionally, some studies also showed *T. congolense* collected from tsetse fly in Zambia and Cameroon was resistant to diminazene aceturate using molecular tools. This finding showed that *T. congolense*, found in the tsetse fly, which had never previously been treated with diminazene aceturate, was also resistant to diminazene aceturate [30,31].

For *Babesia*, the reports of babesiosis drug resistance in cattle are relatively limited compared to trypanosomosis. *Babesia bovis* resistance to diminazene aceturate has been studied in Japan where it was found that using diminazene aceturate at dosages lower than the IC50 dose (0.08μM) in the treatment of *B. bovis* resulted in the development of drug-resistant pathogens [9].

For *Anaplasma*, in 2005, a study in the United States found that the treatment of *A. marginale* infection administered with oxytetracycline (based on the criteria recommended by OIE) could not eliminated *A. marginale* infection in beef cattle [32]. Moreover, a study in Iran reported oxytetracycline drug-resistant genes (oxytetracycline-resistance gene; *otr*) in *A. marginale* and *A. centrale* infected cattle. Interestingly, *A. marginale* found *otr* gene greater than *A. centrale* [33]. The situation of blood parasitic resistance in cattle is shown in table 1.

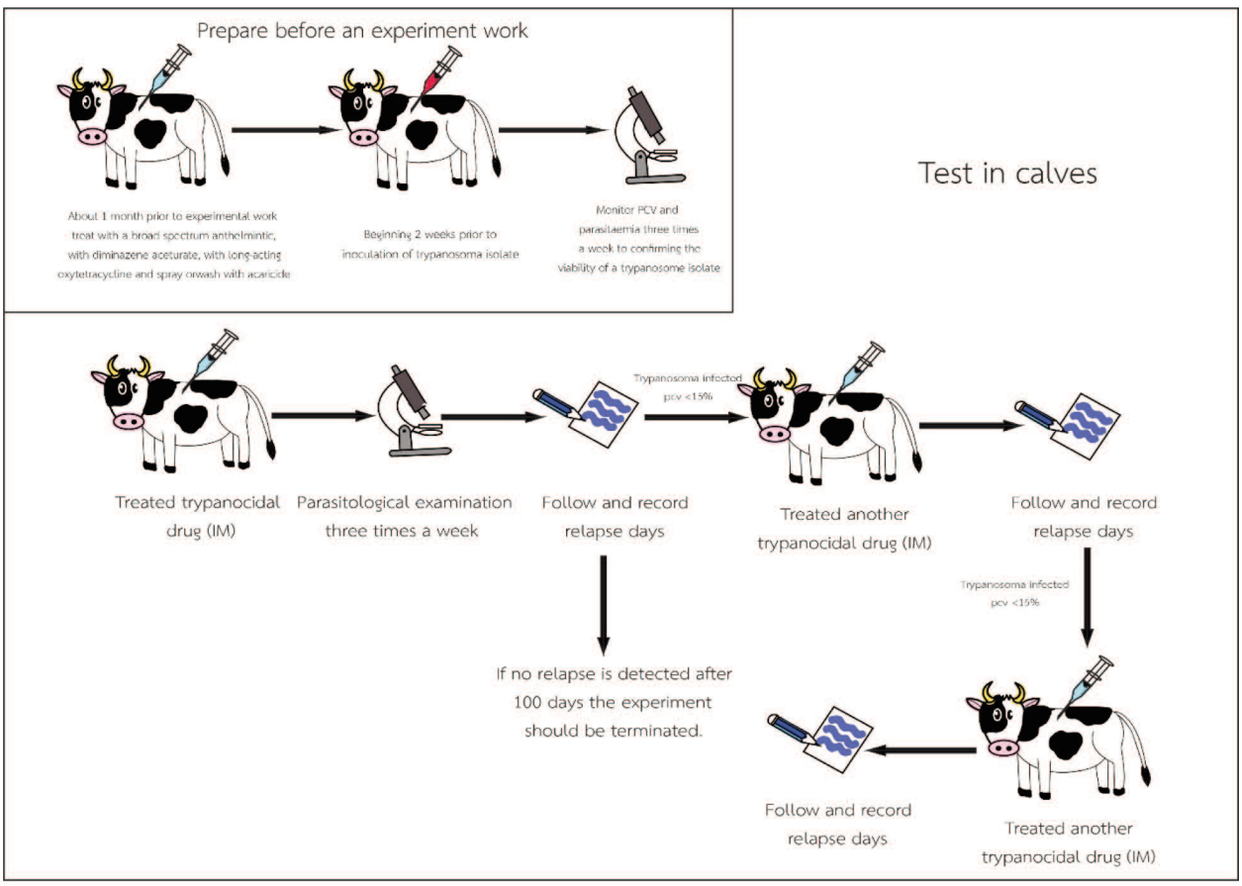

Figure 3. *In vivo* standardized drug sensitivity tests on isolated field-strains in cattle

Drug resistance analysis

There are three commonly used methods for drug resistance analysis: block treatment, *in vivo* standardized drug sensitivity tests on isolated field-strains in mice and cattle and molecular tools [29].

Block treatment it is a follow-up of infected animals administrated with blood parasitic drugs to evaluate the effect of treatment [29]. Drug resistance occurs when treatment is ineffective and the trypomastigote form of the parasites remains present in the buffy coat of the infected animals [18]. Moreover, other parameters such as pack cell volume (PCV) can be supportive for detection of the presence of blood parasites [28]. Post-drug testing may be performed every 2 weeks for a period of 2 to 3 months or according to the experimental criteria [18].

For *in vivo* standardized drug sensitivity tests on isolated field-strains in mice and cattle, the laboratory protocol examines drug resistance in mice first and then in cattle. The experimental method in mice begins with an injection of *Trypanosoma* in mice, and then is followed up by administrated with drug, then examination for *Trypanosoma* in blood of experimental animal until the mice returned to the presence *Trypanosoma* infection again or until the end of the experiment (Fig. 2). The same method is also performed with cattle. The results were able to predict curative doses of the drug needed to eliminate the parasites [34] (Fig. 3). However, the *in vivo* standardized drug sensitivity tests were not successful to detect *T. vivax* as this parasite cannot develop in mice [18].

Molecular tools are able to identify genetic markers related to expression of drug resistance [29]. Several genetic markers practical to recognize diminazene aceturate resistance are *DpnII*-PCR-RFLP [22,29,30], *BclI*-PCR-RFLP [18]. A genetic marker related to isometamidium chloride resistance is *MboII*-PCR-RFLP [18,30].

For the *in vitro* test, this test is experimental in a culture medium with a blood parasite and administered with antiparasitic drugs. Drug-resistant was evaluated from amounts of remain parasite in the culture medium [9].

New approach for blood parasites treatment

Trypanosoma evansi infection has been studied experimentally in laboratories. In the treatment of *T. evansi* infection, diminazene aceturate was combined with other substances such as sodium selenite, vitamin E and tea tree oil which was more effective in reducing parasite compared to treatment with diminazene aceturate alone [35,36]. In addition, co-administration of diminazene aceturate and sodium selenite was more effective compared to treatment with diminazene aceturate alone and treatment with diminazene aceturate combined with both sodium selenite and vitamin E. Treatment efficacy was evaluated from amounts of *T. evansi* in experimental rats, mortality rates and survival rates of infected rats [35]. The efficacy of tea tree oil in the treatment of *T. evansi* was compared among infected mice treated with diminazene aceturate alone, treatment with tea tree oil alone, and treatment with tea tree oil in combination with diminazene aceturate. The results showed that treatment with tea tree oil combined with the therapeutic diminazene aceturate was the most effective [36]. It is possible that the combination of diminazene aceturate with tea tree oil is an alternative treatment for *T. evansi.*

Some plant extracts that have been confirmed for efficacy in treatment of *T. evansi* infection in experimental studies are *Lepidium sativum* seed extract, essential oil a-pinene, essential oil ß-caryophyllene and indigo tree leaves extract [37–39]. *Lepidium sativum* seed extract has been administered in both oral and intraperitoneal routes of *T. evansi* infected mice. The results showed treatment with *Lepidium sativum* seed extract can prevent liver damage due to lower aspartate aminotransferase (AST) and alanine amino-transferase (ALT) values in infected animals. Moreover, histological changes were observed and it was found that administration of *Lepidium sativum* seed extract via intraperitoneal provided better results than oral route [37]. Essential oil of a-pinene and essential oil of ß-caryophyllene have been reported for treatment of *T. evansi* infection in mice which has benefit for longer life in infected mice [38]. An extract from the leaves of the indigo tree had the effect of eliminating *T. evansi*, reducing the number *of T. evansi* in the mice's blood and improving the histology of the infected brain [39]. For treatment of *T. congolense* infection, various vegetable oils including coconut oil, olive oil and safflower oil were reported. The results showed that vegetable oil improved the survival rate of mice and decreased the number of pathogens. These vegetable oils should predominantly be applied in food to control disease [40].

Moreover, the new drug tulathromycin has been reported *in vitro* trials for treatment *B. bovis* and *B. bigemina* infections. The results showed tulathromycin can eliminate and inhibit the growth of *B. bovis* and *B. bigemina* [41].

In conclusion, blood parasitic drug resistance in cattle is one of the largest public health challenges and has been reported for more than half a century. The drug resistance to *Trypanosoma* infection was the most commonly found case while drug resistance to *Babesia* and *Anaplasma* was less common. However, resistance to *Babesia* and *Anaplasma* might be being developed and raising the drug resistance problem. The current situation of blood parasitic drug resistance indicated that no effective of drugs are available. However, new approaches to blood parasitic treatment in cattle have been developed to solve the problem. The effective results are provisional and trials are still being performed in experimental animals and *in vitro*. It has not been confirmed in cattle whether or not the efforts yield good therapeutic efficacy.

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