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The effect of resveratrol supplementation on haematological parameters and trypanocidal efficacy of diminazene aceturate in dogs

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Abstract

Trypanosomosis is a debilitating, fatal disease of man and animals often associated with anaemia. The trypanocides currently used in the management of the disease are far from giving desired results. This study investigated changes in haematological indices and the treatment outcome of diminazene aceturate (DA) against *Trypanosoma brucei* in dogs supplemented with resveratrol. A total of twenty (20) male Nigerian local breed of dogs (NBD) aged 6 to 12 months were used for the study. The dogs were randomly assigned into five groups (I-V) of four dogs per group. Group I was uninfected and unsupplemented; group II, was infected, untreated, and unsupplemented; group III, infected unsupplemented, treated with DA, group IV was infected and supplemented but untreated with DA, and group V was infected and supplemented DA-treated. The mean pre-patent period of Trypanosoma infection was 5.75±0.96 and 9.00±0.82 days for the infected unsupplemented and the infected resveratrol-supplemented groups, respectively. There was a complete parasite clearance from peripheral blood within 24-48 hours following treatment with DA on day 10 post-treatment (PT) in the supplemented and 24-72 hours in the unsupplemented treated groups. The supplemented treated did not show any relapse of infection, whereas the un-supplemented, DA-treated showed relapse on day 25 PT. It was concluded that resveratrol supplementation enhanced the efficacy of diminazene aceturate with no risk of relapse, minimized the effects of the parasite in the animals, and increased survival time.

Keywords: Diminazene aceturate, Dogs, Haematology, Resveratrol, Supplementation, *Trypanosoma brucei*

Introduction

Resveratrol is a powerful antioxidant found in red grape skin, mulberries, blueberries, pines, peanuts and many plant-derived products (Ibern-Gomez *et al.,* 2001; Burns *et al.,* 2002; Delmas *et al.,* 2006). It is also

produced by some plants to protect them against environmental stress and infectious agents (Burns *et al.,* 2002). Numerous studies both *in vitro* and *in vivo* have continued to describe different biological impacts and protective effects of resveratrol, including antioxidant, cardioprotective, anti-ageing, anti-platelet aggregation, anticancer, anti-diabetic, anti-inflammatory and immunomodulatory effects (Pervaiz, 2001; Frojdo *et al.,* 2007; De la Lastra & Villegas, 2007; Singh *et al.,* 2015). It has also been reported to possess antibacterial, antifungal and antiviral activities (Vestergaard & Ingmer, 2019).

As a natural antioxidant, resveratrol is considered more effective than other antioxidants, vitamins C and E (Murcia & Martinze-Tome, 2001). Resveratrol has also been used as a feed additive and supplement in animal production (Alagawany *et al.,* 2015). Birds fed diet supplemented with resveratrol showed an increase in feed consumption and body weight gain (Alagawany *et al.,* 2015). It is therefore proposed that resveratrol supplementation could have beneficial effects in the management of debilitating and immunosuppressive diseases such as trypanosomosis (Odo *et al.,* 2020).

Animal trypanosomosis remains a debilitating protozoan disease and constitutes a substantial source of morbidity and mortality in tropical and sub-Saharan Africa (Stevens & Brisse, 2004; Espuelas *et al.,* 2012). World health organization (WHO) has described trypanosomosis as a serious disease lacking effective control measures, and all mammalian hosts are susceptible to the infection (Cattand *et al.,* 2005). The disease is characterized by parasitaemia, fever, anaemia, loss of condition and reduced productivity (Abenga *et al.,* 2002; Fajinmi *et al.,* 2007).

Over past decades, prevention and control of animal trypanosomosis have relied mainly on chemotherapy and chemoprophylaxis, together with vector control measures. The current chemotherapeutic treatments widely used are far from satisfactory due to limitations such as severe toxicity, acquired resistance, poor efficacy, and lack of availability of the drugs. In addition, the route and schedule of administration was not well adapted to the field conditions, antigenic variation and subsequent escape from immune clearance (Barrett *et al.,* 2004; Espuelas *et al.,* 2012). This study was therefore designed to investigate the effects of resveratrol supplementation on haematology and the outcome of diminazene aceturate treatment against *T. brucei* in local Nigerian breed of dogs.

Materials and Methods

Experimental animals

A total of twenty (20) male dogs between the ages of 6 and 12 months were used for the study. The dogs were purchased from Orba market in Enugu State, Nigeria. On arrival at the animal house, they were allowed to acclimatize for 14 days before the commencement of the experiment and blood and faecal samples were collected and examined for the presence of haemo and gastrointestinal-parasites. Animal studies complied with the ethical procedure of the Animal Use and Care Committee, College of Veterinary Medicine, Michael Okpara University of Agriculture, Umudike, which corresponds with NIH guidelines (NIH, 1996).

Experimental procedure

The dogs were divided into five groups of four dogs each. Group I (Control) was uninfected, and unsupplemented with resveratrol. Group II was infected unsupplemented and untreated, while groups III, IV and V were infected with unsupplemented diminazene aceturate (DA) treated, infected resveratrol-supplemented, untreated with DA and infected resveratrol-supplemented, and DA-treated, respectively.

Trypanosome infection

Trypanosoma brucei were obtained from the Department of Veterinary Parasitology and Entomology, University of Nigeria, Nsukka. Before been used for the infection of the experimental animals, the trypanosomes were first inoculated into a donor dog intraperitoneally (ip) at a dose of 1.5×10^6 parasites per millilitre of blood diluted with normal saline. The same dose and route of administration were used for the experimental animals. The number of infective trypanosomes was determined using the rapid matching method of Herbert & Lumsden (1976). Parasitaemia was monitored in each of the infected dogs daily from day 2 post-infection (PI) till patency and weekly thereafter using buffy coat microscopy as described by Murray *et al.* (1977). The animals were also monitored for mortality, parasite clearance time, and relapse of the infection. The experiment lasted for a period of sixty (60) days post-infection.

Resveratrol and diminazene aceturate administration

Ninety-nine percent pure resveratrol powder (Candlewood Star Incorporated Danbury, Connecticut, USA) was used for the study. Trans-resveratrol, due to its low solubility in water, was suspended in 10 g/L of carboxymethylcellulose (CMC), and administered orally at a dose of 100 mg/kg body weight as reported by Odo *et al.* (2020). Groups IV and V were pre-treated with resveratrol 7

days before infection and 14 days post-infection. Groups III and V were treated on day 10 post-infection (PI) (peak parasitaemia) with diminazene aceturate intramuscularly (IM) at the dose of 7 mg/kg body weight. The control group received 10 g/L of carboxymethylcellulose (CMC) orally.

Determination of haematological parameters

Haematological parameters; Red blood cell count (RBC count), Packed cell volume (PCV), Haemoglobin Concentration (HB), Total white blood cell (WBC) and differential cell counts (lymphocytes, neutrophils, monocytes and eosinophils) were analyzed using an Automated Haematology Analyser (model 2800 BC produced by Mindray Company, India) following standard procedures outlined by the producer.

Statistical analysis

Data obtained from the study were expressed as mean ± standard error of mean and analyzed using the one-way analysis of variance (ANOVA), and variant means were separated by Duncan's multiple range test in SPSS version 20 (Duncan, 1955). A significant difference was accepted at a probability level of $p \leq 0.05$.

Results

The mean pre-patent period (MPP) of infection was 5.75±0.96 (5-7) and 9.00 ± 0.82 (8-10) days between infected unsupplemented and supplemented infected respectively. The MPP of infected between unsupplemented and supplemented groups showed significant difference ($p < 0.05$). There was a complete parasite clearance from peripheral blood within 24-48 (Mean: 36.00±13.86) hours following treatment with DA in the supplemented infected group and 24-72 (Mean: 54.00 ± 22.98) hours in the unsupplemented groups, but, the difference was not significant ($p > 0.05$) between the groups. The supplemented DA-treated group did not show any relapse of infection, whereas the unsupplemented DA-treated showed relapse on day 25 post-treatment. The proportions of dogs surviving post-infection and post-treatment were summarized in Table 1. Death increased progressively among the infected untreated group till the end of the experiment. The survivability did not differ significantly ($p>0.05$) among the groups infected and treated singly withdiminazene aceturate, resveratrol and a combination of resveratrol and diminazene aceturate.

The mean red cell parameters (PCV, HB and RBC) of the infected untreated group was significantly ($p<0.05$) lower than those of the other groups. Resveratrol-supplemented DA-treated group was significantly ($p<0.05$) higher than all the other infected groups and compared with the control. The mean PCV of the infected resveratrol-supplemented

Table 1: Parasitaemia, survivability, parasite clearance time and relapse of infection of resveratrol-supplemented *T. brucei*-infected dogs treated with diminazene aceturate

Days post-infection	Groups				
	Uninfected untreated (control)	Infected untreated unsupplemented	Infected treated with DA	Infected treated with resveratrol	Infected treated with resveratrol and DA
0	0/4	0/4	0/4	0/4	0/4
7	0/4	4/4	4/4	0/4	0/4
14	0/4	4/4	4/4*	4/4	4/4*
21	0/4	4/4	0/4	4/4	0/4
28	0/4	3/3	0/4	4/4	0/4
35	0/4	3/3	4/4**.	4/4	0/4
42	0/4	1/1	4/4	4/4	0/4
49	0/4	1/1	4/4	4/4	0/4
56	0/4	1/1	4/4	3/3	0/4
63	0/4	1/1	4/4	3/3	0/4

0 - Indicates the day of infection

*Indicates day of treatment with diminazene aceturate (DA) (Day 10 post-infection)

** indicates day of relapse of infection (25 days post-treatment)

Numerator indicates number of dogs parasitaemic

Denominator indicates the number of dogs infected (variations is due to mortalities)

group was significantly ($p<0.05$) higher on day 7 post infection and significantly ($p<0.05$) lower on day 21 post infection when compared with the DA-treated group (Figure 1). The mean HB concentration of supplemented untreated group and unsupplemented DA-treated group did not differ significantly ($p>0.05$) from day 35 PI (Figure 2). The mean RBC counts from day 35 PI was significantly ($p<0.05$) higher in the group supplemented with resveratrol and treared DA, when compared with the group treated with only resveratrol (Figure 3).

The mean TWBC counts of the infected untreated group was significantly ($p<0.05$) higher than all the infected groups on days 7, 14 and 21 PI. The mean TWBC counts of the groups supplemented with only resveratrol and a combination of resveratrol and DA did not differ significantly ($p>0.05$) on days 14, 21, 28 and 35 PI, but were significantly ($p<0.05$) lower than the infected and treated with DA alone (Figure 4). The mean neutrophil counts of the infected groups did not differ significantly ($p<0.05$) from the control on days 7 and 14 PI. On days 35, 42, 49 and 63 PI, the infected resveratrol-supplemented and the resveratrol, DA-treated groups were significantly ($p<0.05$) higher than the infected DA-treated group (Figure 5). The mean lymphocyte counts of the infected groups did not differ significantly ($p>0.05$) from the control group on days 7 and 14 PI. In contrast, infected resveratrol-supplemented and resveratrol DA-treated groups showed significantly ($p<0.05$) lower lymphocyte counts on days 35 and 42 PI (Figure 6).

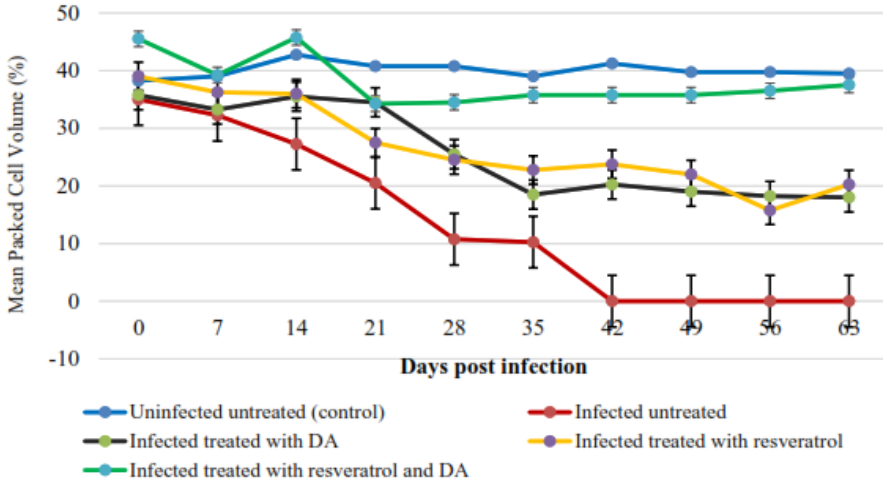

Figure 1: Mean packed cell volume (%) of resveratrol-supplemented *T. brucei-infected* dogs treated with diminazene aceturate

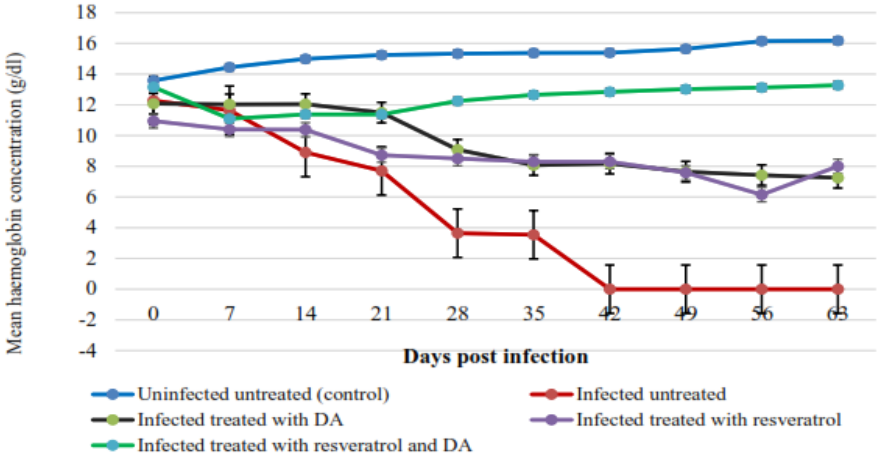

Figure 2: Mean haemoglobin concentration (g/dl) of resveratrol-supplemented *T. brucei*-infected dogs treated with diminazene aceturate

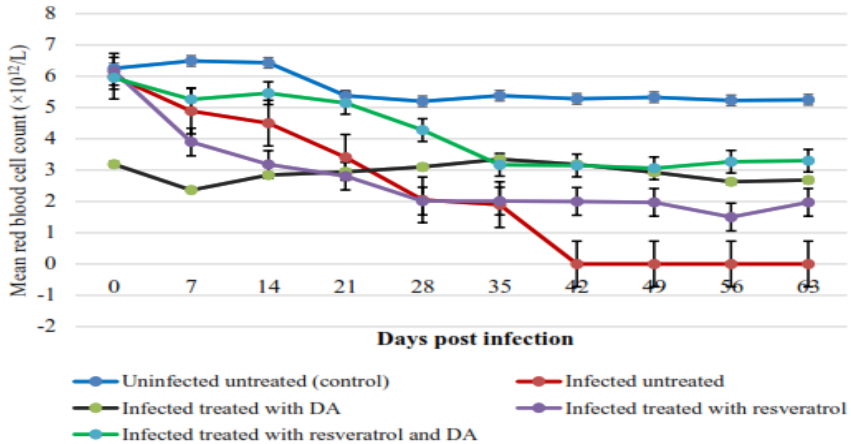

Figure 3: Mean red blood cell count ($\times10^{12}$/L) of resveratrol-supplemented *T. brucei*-infected dogs treated with diminazene aceturate

Discussion

Resveratrol is one of the naturally occurring compounds with a wide range of health benefits. Results obtained from numerous *in vitro* studies have encouraged scientists to continuously conduct investigations with animals and clinical trials on humans (Gerszon *et al.,* 2014). In the present study, the mean pre-patent period was significantly increased in the resveratrol-supplemented groups compared with the unsupplemented groups. This result suggests that resveratrol was able to delay the onset of parasitaemia, unlike other antioxidants, vitamins C and E (Murcia & Martinze-Tome, 2001). The result, however, is at variance with other workers (Eghianruwa, 2012; Eze *et al.,* 2013; Eze *et al.,* 2015) who did not observe any significant effect in *T. brucei-infected* rats supplemented with selenium, vitamin C and zinc, respectively. The parasites was cleared faster in the supplemented treated group than in the unsupplemented treated group. In addition, relapse occurred in the unsupplemented treated group on day 25 post-treatment. This result corroborates the findings of (Igbokwe *et al.,* 1998; Umar *et al.,* 2000; Ihedioha & Anwa, 2002) who used antioxidants to increase the efficacy of diminazene aceturate and reverse the pathological conditions caused by trypanosome infection. It was also observed from this study that the outcome of treatment with resveratrol and DA

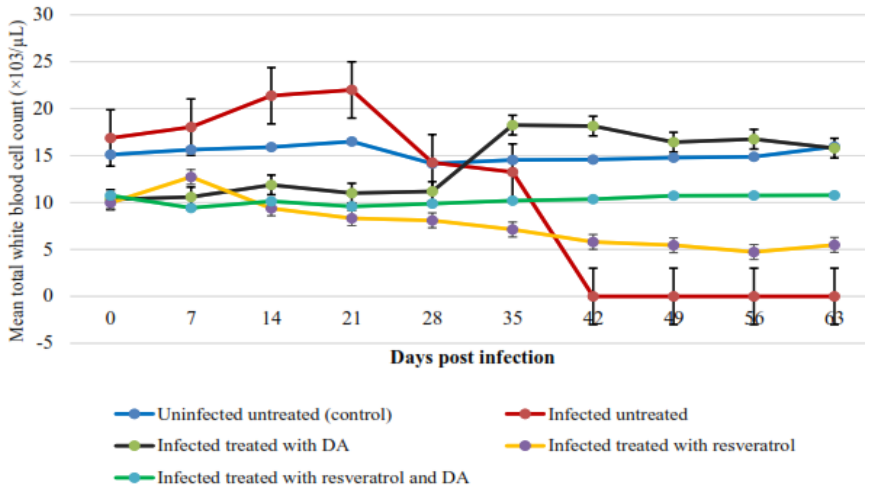

Figure 4: Mean total white blood cell count (×10^3/µL) of resveratrol-supplemented *T. brucei*-infected dogs treated with diminazene aceturate

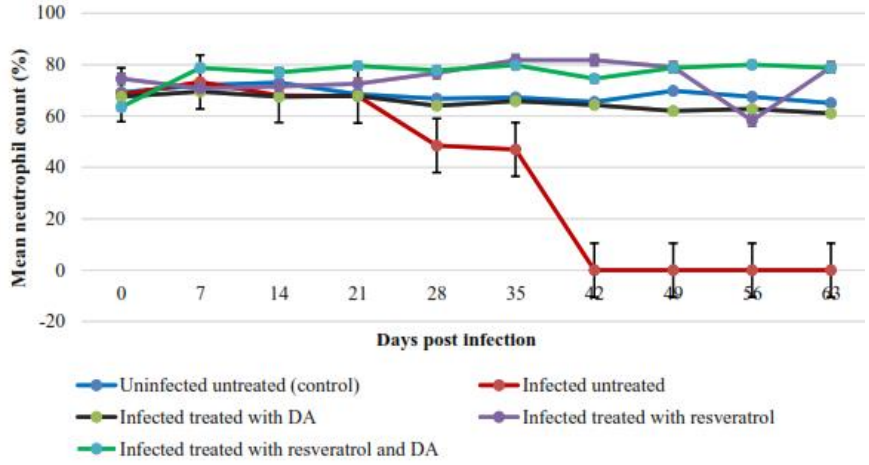

Figure 5: Mean neutrophil counts (%) of resveratrol-supplemented *T. brucei*-infected dogs treated with diminazene aceturate

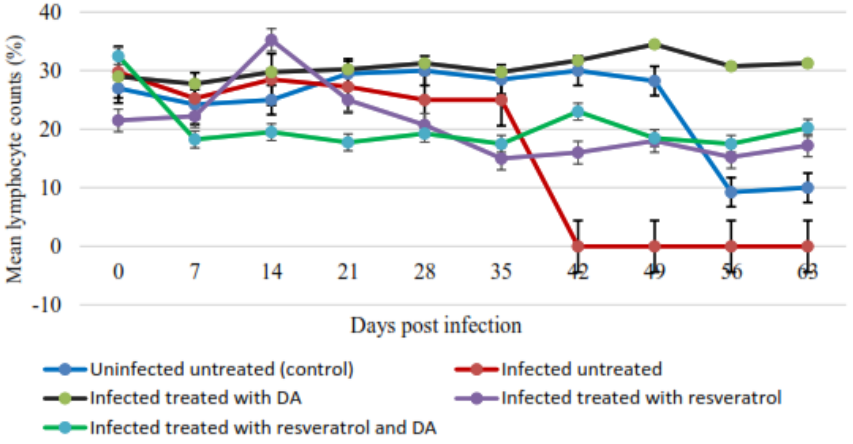

Figure 6: Mean lymphocyte counts (%) of resveratrol-supplemented *T. brucei-infected* dogs treated with diminazene aceturate

resolved the issue of relapse infection, compared to other previous studies with DA and other antioxidants where relapse of infection occurred after treatment (Eghianruwa & Oridupa, 2018).

The prolonged survival time seen in the supplemented untreated group in this study could be attributed to the immunomodulatory and antioxidant effects of resveratrol (Sahin *et al.,* 2010). This result is similar to the previous work done by Eze *et al.* (2013), who demonstrated the ability of selenium supplementation to increase the survival time of *T. brucei-infected* rats. The increased survivability of the supplemented infected untreated group may also be associated with the anti-ageing and anti-stress properties of resveratrol (Baxter, 2008). It has been reported that resveratrol reversed ageing and cell death in liver of old animals by maintaining high levels of antioxidant activities (Tung *et al.,* 2013). Similarly, resveratrol supplementation for horses has also been shown to ameliorate oxidative stress due to ageing and lameness in horses (Ememe *et al.,* 2015).

The mean red cell parameters (PCV, HB and RBC) counts of the resveratrol-supplemented, diminazene aceturate treated group was significantly ($p>0.05$) higher than those of the other infected groups and comparable with the control. This result agrees with other pervious workers (Eghianruwa, 2012; Eghianruwa & Oridupa, 2018) that antioxidants enhance the therapeutic activities of diminazene aceturate. Similarly, Atmaca *et al.* (2014) and Highab *et al.* (2016) reported that resveratrol supplementation reversed fluoride and lead induced toxicity associated with haematological derangements respectively. The mean PCV, HB and RBC counts of the infected unsupplemented, untreated group was significantly lower ($p<0.05$) than that of the control. This result is in consistent with the previous study conducted by Rashid *et al.* (2008) who stated that anaemia is a cardinal sign of trypanosomosis. Anaemia in trypanosomosis is an indication of oxidative stress and depletion of antioxidant status, which has been suggested to play a major role in the pathogenesis of African animal trypanosmosis (Igbokwe *et al.,* 1994; Taiwo *et al.,* 2003; Akanji *et al.,* 2009).

Leucocytes are markers for assessing the levels of immune response under stressful conditions as they are important in protecting the body against infections agents (Hardie *et al.,* 1991; Ufele *et al.,* 2007). In this study the total leucocytes counts were significantly ($p<0.05$) lower in the infected resveratrol-supplemented groups compared with the infected unsupplemented groups. This result supports previous finding that resveratrol may have played a role in the leucocytic response, recovery and management of parasite load by improving the immune response (Ufele *et al.,* 2007). The leucocytosis observed in the infected untreated group was attributed to the immune response associated with African trypanosomosis which is consistent with other workers (Anosa *et al.,* 1997; Ndoutamia *et al.,* 2002), but disagrees with (Kobo *et al.,* 2014) who observed decreased total leucocyte counts in infected untreated rats.

In conclusion, this study showed that resveratrol enhanced the ability of trypanosome infected animals to tolerate parasite load by conserving anaemia, mortality rate, and increased survival time. Furthermore, resveratrol supplementation will enhance the efficacy of diminazene aceturate and reduce the risk of relapse. We therefore, recommend that diets of animals in endemic areas should be supplemented with resveratrol.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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