

## Research Article

# Effect of Resveratrol on Haematological Changes in Diabetic-Malaria Infected Wistar Rats

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## ABSTRACT

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The effect of resveratrol on haematological changes in diabetic-malaria infected rats was investigated. Five of six groups of male Wistar rats were induced with type 2 diabetes, followed by inoculation with malaria parasites. Four groups of the diabetic-malaria infected rats were orally given: low dose resveratrol (50 mg/kg), high dose resveratrol (100 mg/kg), Metformin (100 mg/kg) and Artesunate (5 mg/kg) respectively for six days after malaria inoculation. Administration of resveratrol, metformin and artesunate to diabetic-malaria infected rats significantly ( $p < 0.05$ ) decreased the blood glucose level (BGL) on days 3 and 6 post-inoculation. The high dose resveratrol (RSV 100) group showed a significant ( $p < 0.05$ ) increase in red blood cell counts, although a significant ( $p < 0.05$ ) decrease of Packed Cell Volume was recorded in the low dose resveratrol group. There was no significant ( $p > 0.05$ ) difference for the values of total WBC counts across the four groups of the diabetic-malaria infected rats, but the differential WBC counts (dWBCC) were significantly ( $p < 0.05$ ) affected. High dose resveratrol administration significantly ( $p < 0.05$ ) reversed the dWBCC. The diabetic-malarial infected group showed significant ( $p < 0.05$ ) decrease in average RBC; the average parasites and average infected RBC counts were significantly ( $p < 0.05$ ) higher than that in the resveratrol groups. While, Metformin and Artesunate groups showed a further decline in parasitaemia. These findings indicate that Resveratrol decreased BGL and improved hematological parameters and suppressed parasitaemia in diabetic-malarial infected rats.

**Keywords:** Diabetes, Haematological Indices, Malaria, Parasitaemia, Rat, Resveratrol

## INTRODUCTION

Diabetes and malaria comorbidity allows the study of both diseases as clusters rather than isolate entities, and altered hematological parameters are a common complication associated with these illnesses (Arkew *et al.*, 2021). Interestingly, resveratrol has been reported to have diverse effects on diabetes, malaria and the hematological system (Zhu *et al.*, 2017; Elshaer *et al.*, 2018). Resveratrol (RSV) 3, 4, 5-trihydroxystilbene is a naturally occurring polyphenol

found in different plant species. Enormous amounts of resveratrol are found in berries, grapes, peanuts and are also in tablets form (Soliman *et al.*, 2017). Resveratrol increases the repopulation capacity of haemopoietic stem cells and possesses useful blood schizontocidal action (Remmele *et al.*, 2014; Elshaer *et al.*, 2018). Also, antidiabetic action of resveratrol such as improved glucose uptake, insulin resistance and antioxidant activities have been reported (Aggarwal *et al.*, 2004; Zhu *et al.*, 2017). Studies by Lee *et al.* (2008) reported that the antimalarial activity of

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*Pleuropterus ciliinervis* against *P. falciparum* *in vitro* is attributed to RVS.

*Plasmodium berghei* is a widely used mouse malaria model and a dominant tool for reverse genetic studies in malaria (Jambou *et al.*, 2011). Malaria directly affects the haematopoietic system, by decreasing erythropoiesis and increases parasitaemia in RBC (Omodeo-Sale *et al.*, 2005). Also, studies have reported that type 2 diabetics have an increased risk of infection with *Plasmodium falciparum*, which is associated with increases in glucose concentration (Danquah *et al.*, 2010).

Moreover, Danquah *et al.* (2010) reported that an increased risk for *P. falciparum* infection occurs by 5% with each mmol/L increase in blood glucose. A recent study reported that the growth and proliferation of the malaria parasites were impaired below 5.5 mM (99 mg/dL) of glucose concentration and was unaffected at concentrations of 5.5 – 27.7mM glucose (Humeida *et al.*, 2011). Both studies imply that, the elevated blood glucose levels among patients with type 2 diabetes affords a favorable environment for the replication of *Plasmodium* species and thus increases parasitaemia. Furthermore, a long-term hyperglycemia is associated with the formation of advanced glycation end products (AGEs), a causative factor of haematological changes in diabetes (Kaur *et al.*, 2018). Anemia is a common haematological change in patients with T2DM and characterized by a decrease in the RBC count, hemoglobin (Hgb) and haematocrit (Hct) level (Gauci *et al.*, 2017). Other haematological changes encountered in T2DM patients, may manifest as immunological and coagulation problems (Antwi-Baffour *et al.*, 2018).

The search for an optimal therapy for T2DM without deleterious side effects led to the detection of the hypoglycemic effect of resveratrol. However, various researches focused on the effect of resveratrol on diabetes or malaria independently, which is perhaps responsible for the apparent dearth of data in diabetes and malaria co-morbidity, and as well limited information on haematological disorders in diabetic-malaria comorbidity. This paper therefore, investigates the effect of resveratrol on some haematological changes and parasitaemia in diabetic Wistar rats co-infected with *Plasmodium berghei* parasites.

## MATERIALS AND METHODS

### Chemicals and reagents

Trans-resveratrol (MR180519, MegaResveratrol, Danbury); Ridplas Artesunate; Streptozotocin (Santa Cruz biotechnology, Dallas texas); ketamine and diazepam. Didigital glucometer (Accu-Chek Advantage, Roche

Diagnostic, Germany). All chemicals and reagents used for the study were of analytical grade.

### Source of *Plasmodium berghei*

The parasite (chloroquine-resistant *P. berghei*) was obtained from animal house of Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria.

### Preparation of high-fat diet

The High-Fat Diet (HFD) was prepared by mixing the grower mash feed (constitutes; fats 18%, proteins 54% and carbohydrates 28%) with margarine (99.9% fats) and groundnut meal in the (percentage) ratio of (50%) 500 g of feed to (25%) 250 g of margarine and (25%) 250 g of ground nut meal, a modification of the composition described by Okoduwa *et al.* (2017) and Alex *et al.* (2019).

### Induction of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) was induced according to the method described by Alex *et al.* (2019). The animals were fed with HFD along with 20% fructose solution as drinking water for eight (8) weeks, after which they were fasted overnight and given a single intraperitoneal injection of 30 mg/kg streptozotocin. On the 3<sup>rd</sup> day (72 hours) and the 5<sup>th</sup> day after STZ administration, the rat's tail vein blood was used for assessing the blood glucose level using glucose test strips and digital glucometer. The results were expressed in mg/dL of blood (Rheney and Kirk, 2000). Only rats with blood glucose levels  $\geq$  200 mg/dL were considered diabetic.

### Inoculation of Malaria

The inoculation of malaria was carried out by the method as described by Fernanda *et al.* (2010). Blood from a donor mouse with a parasitaemia level above 20% was drawn into a heparinised syringe and diluted with phosphate-buffered saline (pH 7.2). The infection was then initiated by injecting 0.2 mL of the parasite preparation from the donor mouse to the experimental rats (diabetic rats) via the intraperitoneal route. From the 3<sup>rd</sup> day (72 hours after inoculation), daily thin blood films stained with Giemsa were prepared from tail blood of each rats till the 6<sup>th</sup> day, to monitor the parasitaemia level. The packed cell volume (PCV) was also measured on day 0, prior to inoculation and on the sixth day.

### Animals and experimental design

A total of thirty-six Male Wistar rats, 6-8 weeks old (150-180g), were acclimatized to the laboratory conditions for two weeks. The rats were randomly divided into six (6) groups (n=6). One of the six groups (group 1) was maintained as normal control group with normal feed and

drinking water *ad libitum*; the remaining five groups were induced with type 2 diabetes followed by inoculation with *Plasmodium berghei* parasite to induce malaria. One group (group 2) of the diabetic-malaria infected rats served as the diabetic-malaria control group; two groups (groups 3 and 4) were each given oral dose of resveratrol at 50 mg/kg or 100 mg/kg (Moon and Sim, 2008); the remaining two groups (groups 5 and 6) were given metformin (100 mg/kg) (Tikoo *et al.*, 2016) and artesunate (5 mg/kg) (Clark *et al.*, 2004) respectively. Oral administrations of resveratrol, metformin and artesunate commenced immediately after inoculation and concluded on the 6<sup>th</sup> day post-inoculation.

### Estimation of parasitaemia

Blood sample was collected from tail snip of each rat (Fernanda *et al.*, 2010). Blood smears were applied on microscope slides, fixed with absolute methanol for 15 min, and stained with 15% Geimsa stain at pH 7.2 for 15 min. The stained slides were washed gently using distilled water and air dried at room temperature (25-26°C). Then, each stained slide was examined under the microscope with an oil immersion objective of 100 x magnification power to investigate parasite load. The number of parasitised erythrocytes in about 10-50 fields were counted twice and the average computed to give the parasitaemia of each rat (Fernanda *et al.*, 2010). The parasitaemia level was determined by counting minimum of five fields per slide.

### Sample collection

After the experimental period, all the rats were anaesthetised using 100 mg/kg body weight of ketamine and 5 mg/kg body weight of diazepam followed by cervical dislocation. Blood samples were collected in potassium ethylene disulphide tetraacetic acid (K<sub>2</sub> EDTA) bottles.

### Haematological indices

Standard technique was used in estimation of total leucocytes and erythrocytes counts using Neubauer hemocytometer; Feinoptik, differential leucocytes count was done by Leishman's staining method. The PCV was estimated by centrifuging blood in haematocrit tube and reading it using a hematocrit reader (Ghai, 1999).

### Statistical analysis

All data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Values were expressed as mean  $\pm$  S.E.M. P values less than 0.05 (P < 0.05) was considered as accepted level of significant difference between the groups.

## RESULTS

Table 1 shows the result for blood glucose levels (BGL), across groups from before diabetes induction, on the day of malaria inoculation, the 3<sup>rd</sup> and 6<sup>th</sup> days post-inoculation. Blood glucose level was significantly (p < 0.05) increased in the Diabetic-malarial Control group on the 3<sup>rd</sup> and 6<sup>th</sup> Days post-inoculation compared to the Normal Control group. Separate doses of resveratrol, metformin (Met) and artesunate (Arte) treatments significantly (p < 0.05) decreased BGL on days 3 and 6 post-inoculation. Also, the effect of low dose resveratrol (RSV. 50) on BGL on day-6, is comparable to that conferred by metformin.

The effect of time and treatment were statistically significant (p < 0.05) on the change in blood glucose level in the treated groups (Figure 1) F (2.557) = 45.886, P= 0.0005 and F (7.00) = 5.687, P= 0.0005. Similarly, the interaction between time and treatment on mean blood glucose levels on days 0, 3 and 6 were significantly higher compared to the baseline before diabetes induction F (17.897) = 5.439, P= 0.000.

The result in Table 2 shows that red blood cell (RBC) count was significantly (p < 0.05) decreased in Diabetic-malarial control group compared to normal-control group. Administration of the low dose resveratrol (RSV 50) and Arte significantly (p < 0.05) reversed the values of RBC count, however, the high dose RSV (RSV 100) and Met administration significantly (p < 0.05) increased RBC counts further than that conferred by RSV 50. Table 2 also shows the fluctuations in the packed Cell Volume (PCV) (%) across the groups for day-0 and day-6. All the diabetic-malarial infected groups showed significant (p < 0.05) decrease in PCV on days 0 and 6, compared to the normal control group. The groups given RSV 100, Metformin or Artesunate showed no significant (p > 0.05) difference in PCV compared to diabetic-malarial control group except for the group given RSV 50 which indicated a significant (p < 0.05) decrease in PCV.

The result in Table 3 indicates a significant (p < 0.05) decrease in the total WBC count in all the diabetic-malarial infected groups when compared to the normal control group. However, RSV, Met and Arte administration did not ameliorate the effect of diabetic-malarial infection on total WBC count. Table 3 also presents the results of Differential White Blood Cell count (dWBCC), the Diabetic-malarial Control group compared to the normal control group showed as follows: significant (p < 0.05) increases in neutrophils and monocytes counts; significant (p < 0.05) decreases in basophils and lymphocytes count and no significant (p > 0.05) difference in eosinophil counts. However, groups

treated with separate doses of RSV indicated a significant ( $p < 0.05$ ) reversal of the increases in neutrophils and monocytes counts, while RSV 100 group alone showed a significant ( $p < 0.05$ ) reversal of the decreases in basophils and lymphocytes count. But, the groups treated with Metformin or Artesunate, showed no significant ( $p > 0.05$ ) effect on neutrophils, monocytes and lymphocytes counts.

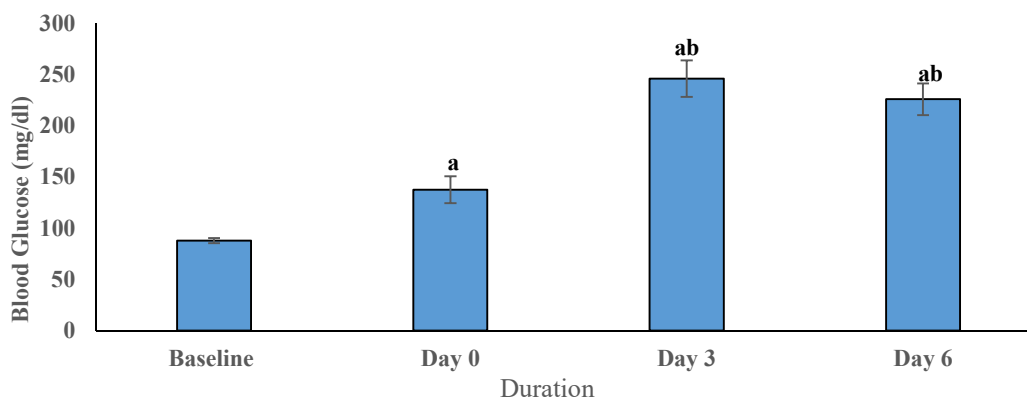
The result of average RBC value in five fields as depicted in Table 4 indicates that diabetic-malarial infection caused a significant ( $p < 0.05$ ) decrease in average RBC value across days 3, 4, 5 and 6. However, on the 6<sup>th</sup> day, the respective dose of Resveratrol and Metformin significantly ( $p < 0.05$ ) increased the average RBC values while Arte significantly ( $p < 0.05$ ) decreased it.

Table 5 shows the Average malaria parasites count in five fields. The average malaria parasites in diabetic-malarial control group was significantly ( $p < 0.05$ ) higher on days 5 and 6 across the groups. Resveratrol (50 mg/kg or 100 mg/kg) groups showed a significant ( $p < 0.05$ ) decline. And, Metformin and Artesunate groups recorded a further decline in average parasites count significantly ( $p < 0.05$ ). Similarly, the average infected RBC count in five fields as shown in table 6, indicates that the diabetic-malarial control group had the highest value on the sixth day and was significantly ( $p < 0.05$ ) decreased by resveratrol groups, though Metformin and Artesunate groups showed further decline in average infected RBCs count across days 3 to 6.

**Table 1.** Effect of Resveratrol on Blood Glucose Levels in Diabetic-Malarial Infected Rats

Experimental Groups (n=5)	Baseline BGL (mg/dL)	Day 0 BGL (mg/dL)	Day 3 BGL (mg/dL)	Day 6 BGL (mg/dL)
N Control	84.80 ± 3.01 <sup>a</sup>	68.80 ± 1.58 <sup>a</sup>	83.20 ± 2.96 <sup>a</sup>	122.40 ± 24.51 <sup>a</sup>
DM Control	78.00 ± 4.96 <sup>a</sup>	102.40 ± 14.22 <sup>b</sup>	338.60 ± 59.35 <sup>b</sup>	408.00 ± 85.79 <sup>b</sup>
RSV (50 mg/kg)	108.00 ± 13.70 <sup>b</sup>	123.40 ± 15.98 <sup>b</sup>	166.60 ± 24.32 <sup>c</sup>	87.20 ± 3.44 <sup>c</sup>
RSV (100 mg/kg)	78.60 ± 4.24 <sup>a</sup>	98.80 ± 8.41 <sup>a</sup>	196.80 ± 63.32 <sup>d</sup>	184.60 ± 51.22 <sup>d</sup>
Met (100 mg/kg)	91.40 ± 7.72 <sup>a</sup>	183.20 ± 84.45 <sup>c</sup>	257.80 ± 70.19 <sup>e</sup>	93.20 ± 4.25 <sup>c</sup>
Arte (5 mg/kg)	90.00 ± 5.79 <sup>a</sup>	123.80 ± 18.39 <sup>b</sup>	208.00 ± 34.21 <sup>f</sup>	161.20 ± 33.52 <sup>d</sup>

All values are means ± SEM of five replicates. Values with different superscripts across the groups are significantly different ( $p < 0.05$ ). N= Normal; DM= Diabetic-Malaria; RSV= Resveratrol; Met= Metformin; Arte= Artesunate; BGL= Blood glucose level



**Figure 1.** Relationship Between Blood Glucose and Time for Diabetic-Malaria infected Rats.

Superscripts a and b represents statistical significant effect of time on blood glucose level compared to the baseline and day 0 respectively

**Table 2.** Effect of Resveratrol on Red Blood Cell Counts and Packed Cell Volume in Diabetic-Malaria Infected Rats

Experimental Groups	RBC x10 <sup>6</sup> (μ/L)	PCV (%) Day 0	PCV (%) Day 6
N Control	10.98±0.07 <sup>a</sup>	51.40±1.03 <sup>a</sup>	53.00±0.84 <sup>a</sup>
DM Control	10.26±0.14 <sup>b</sup>	40.20±0.86 <sup>b</sup>	38.60±1.08 <sup>b</sup>
RSV (50 mg/kg)	10.78±0.23 <sup>a</sup>	35.00±1.84 <sup>c</sup>	36.40±1.50 <sup>c</sup>
RSV (100 mg/kg)	11.22±0.14 <sup>c</sup>	41.20±1.24 <sup>b</sup>	39.00±1.30 <sup>b</sup>
Metformin (100 mg/kg)	10.84±0.13 <sup>a</sup>	39.00±0.84 <sup>b</sup>	40.40±0.51 <sup>b</sup>
Artesunate (5 mg/kg)	11.04±0.30 <sup>c</sup>	42.60±1.50 <sup>b</sup>	41.20±0.86 <sup>b</sup>

All values are means ± SEM of five replicates. Values with different superscripts across the groups are significantly different ( $p < 0.05$ ). N= Normal; DM= Diabetic-Malaria; RSV= Resveratrol; Met= Metformin; Arte= Artesunate;

**Table 3.** Effect of Resveratrol on White Blood Cell Counts and Differentials in Diabetic-Malaria Infected Rats

Experimental Groups	WBC x10 <sup>3</sup> (μ/L)	Neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte
N Control	9.68 ± 0.10 <sup>a</sup>	50.00 ± 1.82 <sup>a</sup>	3.00 ± 0.55 <sup>a</sup>	2.20 ± 0.58 <sup>a</sup>	1.40 ± 0.20 <sup>a</sup>	44.80 ± 0.80 <sup>a</sup>
DM control	8.14 ± 0.11 <sup>b</sup>	55.40 ± 3.98 <sup>b</sup>	3.40 ± 0.25 <sup>a</sup>	1.20 ± 0.49 <sup>b</sup>	2.00 ± 0.45 <sup>b</sup>	39.00 ± 3.92 <sup>b</sup>
RSV (50 mg/kg)	8.14 ± 0.12 <sup>b</sup>	51.80 ± 1.39 <sup>a</sup>	3.20 ± 0.37 <sup>a</sup>	1.40 ± 0.25 <sup>b</sup>	1.90 ± 0.25 <sup>b</sup>	41.60 ± 1.86 <sup>b</sup>
RSV (100 mg/kg)	8.42 ± 0.18 <sup>b</sup>	48.20 ± 3.01 <sup>a</sup>	2.20 ± 0.58 <sup>b</sup>	2.40 ± 0.60 <sup>a</sup>	1.60 ± 0.25 <sup>a</sup>	45.60 ± 2.11 <sup>a</sup>
Met (100 mg/kg)	8.10 ± 0.09 <sup>b</sup>	49.20 ± 1.63 <sup>a</sup>	2.40 ± 0.60 <sup>b</sup>	0.80 ± 0.20 <sup>c</sup>	2.80 ± 0.37 <sup>b</sup>	44.80 ± 1.83 <sup>a</sup>
Arte (5 mg/kg)	8.96 ± 0.21 <sup>b</sup>	51.80 ± 3.73 <sup>a</sup>	3.40 ± 0.25 <sup>a</sup>	0.80 ± 0.20 <sup>c</sup>	2.60 ± 0.68 <sup>b</sup>	41.40 ± 4.11 <sup>a</sup>

All values are means ± SEM of five replicates. Values with different superscripts across the groups are significantly different ( $p < 0.05$ ). N= Normal; DM= Diabetic-Malaria; RSV= Resveratrol; Met= Metformin; Arte= Artesunate

**Table 4.** Effect of Resveratrol on Average RBC in Diabetic-Malaria Infected Rats

Experimental Groups	AVG RBC on Day 3	AVG RBC on Day 4	AVG RBC on Day 5	AVG RBC on Day 6
N Control	571.60±23.45 <sup>a</sup>	582.36±27.07 <sup>a</sup>	495.86±15.77 <sup>a</sup>	556.24±18.18 <sup>a</sup>
DM control	428.06±5.38 <sup>b</sup>	432.96±7.17 <sup>b</sup>	463.16±16.39 <sup>b</sup>	437.80±9.05 <sup>b</sup>
RSV (50 mg/kg)	402.32±19.12 <sup>c</sup>	475.60±15.66 <sup>c</sup>	466.70±8.25 <sup>b</sup>	550.80±1.59 <sup>ac</sup>
RSV (100 mg/kg)	450.52±5.150 <sup>d</sup>	436.60±5.69 <sup>b</sup>	492.92±13.52 <sup>c</sup>	533.76±8.25 <sup>c</sup>
Met (100 mg/kg)	501.96±11.42 <sup>c</sup>	458.60±16.66 <sup>c</sup>	455.48±12.14 <sup>b</sup>	457.28±23.47 <sup>d</sup>
Arte (5 mg/kg)	493.20±15.83 <sup>f</sup>	437.78±9.11 <sup>b</sup>	397.20±17.30 <sup>d</sup>	430.32±12.51 <sup>b</sup>

All values are means ± SEM of five replicates. Values with different superscripts across the groups are significantly different ( $p < 0.05$ ). N= Normal; DM= Diabetic-Malaria; RSV= Resveratrol; Met= Metformin; Arte= Artesunate; AVG=Average

**Table 5.** Effect of Resveratrol on Average Parasites in RBC of Diabetic-Malaria Infected Rats

Experimental Groups	AVG RBC Parasites Day 3	AVG RBC Parasites Day 4	AVG RBC Parasites Day 5	AVG RBC Parasites Day 6
N Control	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
DM control	1.08±0.28 <sup>a</sup>	2.72±0.34 <sup>a</sup>	3.08±0.49 <sup>a</sup>	13.68±1.33 <sup>a</sup>
RSV (50 mg/kg)	3.52±0.69 <sup>b</sup>	1.96±0.39 <sup>b</sup>	2.34±0.39 <sup>b</sup>	6.46±0.21 <sup>b</sup>
RSV (100 mg/kg)	0.60±0.20 <sup>c</sup>	4.92±0.59 <sup>c</sup>	2.92±0.19 <sup>b</sup>	8.48±0.46 <sup>b</sup>
Met (100 mg/kg)	0.44±0.13 <sup>c</sup>	2.16±0.17 <sup>ab</sup>	0.92±0.10 <sup>c</sup>	4.00±1.08 <sup>c</sup>
Arte (5 mg/kg)	1.16±0.39 <sup>a</sup>	2.60±0.44 <sup>ab</sup>	0.80±0.11 <sup>c</sup>	1.08±0.34 <sup>d</sup>

All values are means ± SEM of five replicates. Values with different superscripts across the groups are significantly different ( $p < 0.05$ ). N= Normal; DM= Diabetic-Malaria; RSV= Resveratrol; Met= Metformin; Arte= Artesunate; AVG=Average

**Table 6.** Effect of Resveratrol on Average Infected Red Blood Cell in Diabetic-Malaria Infected Rats

Experimental Groups	AVG Infected RBC Day 3	AVG Infected RBC Day 4	AVG Infected RBC Day 5	AVG Infected RBC Day 6
N Control	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
DM control	0.44±0.11 <sup>a</sup>	0.72±0.14 <sup>a</sup>	0.72±0.12 <sup>a</sup>	2.16±0.20 <sup>a</sup>
RSV (50 mg/kg)	1.44±0.16 <sup>b</sup>	0.92±0.22 <sup>a</sup>	1.06±0.11 <sup>a</sup>	1.34±0.15 <sup>b</sup>
RSV (100 mg/kg)	0.24±0.10 <sup>a</sup>	1.16±0.08 <sup>b</sup>	1.36±0.08 <sup>b</sup>	1.56±0.07 <sup>b</sup>
Met (100 mg/kg)	0.20±0.06 <sup>a</sup>	0.60±0.06 <sup>a</sup>	0.92±0.10 <sup>a</sup>	0.84±0.08 <sup>c</sup>
Arte (5 mg/kg)	0.36±0.11 <sup>a</sup>	0.62±0.08 <sup>a</sup>	0.80±0.11 <sup>a</sup>	0.48±0.16 <sup>d</sup>

All values are means ± SEM of five replicates. Values with different superscripts across the groups are significantly different ( $p < 0.05$ ). N= Normal; DM= Diabetic-Malaria; RSV= Resveratrol; Met= Metformin; Arte= Artesunate; AVG=Average

## DISCUSSION

Malaria parasite proliferation increases in type 2 diabetics with haematological disorders arising from the comorbidity (Ch'ng *et al.*, 2021). The effect of resveratrol on some haematological parameters and parasitaemia in a prevailing comorbidity of diabetes and malaria infection in Wistar rats was investigated.

In this study a successful induction of type 2 diabetes was achieved with HFD feeding and low dose STZ injection, which is consistent with earlier studies (Okoduwa *et al.*, 2017; Alex *et al.*, 2019). Similarly, the result of the decrease in BGL by resveratrol, agrees with several studies that reported the hypoglycaemic effect of resveratrol (Liu *et al.*, 2014; Ziu *et al.*, 2018).

The increase in RBC counts by resveratrol following diabetic-malarial infection in rats is also evident in the result of average RBC counted in five fields per slide for determination of parasitaemia level. Accordingly, resveratrol potentially has the ability to alleviate anemia in diabetic malaria comorbidity. Equally, anemia in type 2 diabetics is a common haematological change and characterised by a decrease in the RBC count, and PCV (Gauci *et al.*, 2017). Although a decrease in PCV value was observed in diabetic-malarial infected groups, but it was not improved by resveratrol in the present study. Possibly, the anemia might be attributed to hyperglycaemic non-enzymatic glycation of RBC membranes as reported by Ekperikpe *et al.* (2018). The changes in differential White Blood Cells, precisely the neutrophils, monocytes and lymphocytes were improved by high dose of resveratrol even though, the total WBC count was unaffected. It therefore, implies that RSV has the potential to react to infectious and immune agents. These finding was similarly observed in studies reported by Ola-Davis *et al.* (2018) on the effects of resveratrol. However, this study contradicts other works on malaria (Akinpelu *et al.*, 2019) and STZ induced diabetes (Ekperikpe *et al.*, 2018) where WBCs were markedly increased.

The degree of malaria parasitaemia provides information on the severity of infection and on the response to treatment, of which in the present study, the average parasites and average infected RBC count indicates that resveratrol suppressed the proliferation of *P. berghei* and decreased the value of parasitised RBC. This could be an evidence of resveratrol's blood schizontocidal action thus inhibiting the proliferation of the plasmodium parasite. This agrees with the studies of Moon and Sim (2008) that indicate the resveratrol's schizontocidal effect. Conversely, the decrease in parasitaemia level in diabetic-malarial infected rats in our study clearly suggest that replication of *Plasmodium* species depends on blood glucose concentration and resveratrol which reduced the blood glucose level interfered with growth of the parasites. Furthermore, the elevated level of erythrocytes enhanced by resveratrol can limit the parasite burden. This pleiotropic action of resveratrol therefore offers additional information on changes in haematological parameters and parasitaemia in diabetic-malaria comorbidity in rats.

## CONCLUSION

Resveratrol at low dose had a better hypoglycaemic effect than the high dose; it also suppressed the proliferation of *P. berghei* parasites and improved the hematological indices in a dose dependent manner in diabetic-malarial infected Wistar rats.

## AUTHORS' CONTRIBUTIONS

The research idea was conceived by JA; the bench work and analyses was done by SA as part of his MSc. research, supervised by FAD, FU and JA. The original manuscript was written by FAD. The final review and editing was conducted by JA, JOA and FU. All the authors gave approval of the final revised version and consent for publication.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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