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Effect of sodium acetate on serum activity of glucose-6-phosphate dehydrogenase in *Plasmodium berghei*-infected mice

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Abstract Malaria is a global health problem with severe morbidity and mortality in Sub-Saharan Africa. Resistance of *Plasmodium* spp to the current anti-malaria drugs necessitates further search for novel effective drugs. This study, therefore, investigated the effect of sodium acetate on glucose-6-phosphate dehydrogenase in *Plasmodium berghei*-infected mice. Thirty male Albino mice were randomly distributed into 6 groups, A–F. Animals in Groups B–F were inoculated with *P. berghei*, intraperitoneally. Subsequently, Group C mice were treated with 20 mg/kg chloroquine, while groups D, E and F received 25, 50 and 100 mg/kg sodium acetate, respectively. All treatments were administered orally for 4 days. At the end of the experiment, animals were sacrificed by cervical dislocation and blood was collected via cardiac puncture for the analyses of serum glucose-6-phosphate dehydrogenase (G6PD), uric acid and lipid profile. Our results showed that Sodium acetate (50 and 100 mg/kg) significantly reduced ($p < 0.05$) parasitaemia (67.11% and 77.62%, respectively) than chloroquine (61.73%). Besides, body weight and serum G6PD activity in *P. berghei* infection were improved. Similarly, sodium acetate reduced elevated

serum uric acid. Effects of sodium acetate and chloroquine on biochemical parameters were comparable ($p > 0.05$) but atherogenic lipid ratios were not affected by sodium acetate. These data put together suggested that activity of sodium acetate may be harnessed for development of novel anti-malaria drugs. However, more studies are required to delineate its mechanisms of action.

Keywords Sodium acetate · *Plasmodium berghei* · Uric acid · Lipid profile · G6PD

Introduction

Malaria is a serious disease in both tropics and sub-tropics, especially in Africa and Asia, accounting for 93% of malaria global incidence in 2018 (WHO 2019). Despite a significant reduction in disease transmission in many former high incidence settings, only few areas have become malaria-free. Thus, malaria remains a serious health problem with high morbidity and mortality than any other parasitic infections, especially among children and pregnant women (WHO 2015, 2019). The main pathophysiological consequences of malaria are caused by the asexual blood stage of *Plasmodium* spp. The erythrocytic stage of *Plasmodium* modifies host erythrocyte and ingests 60–80% of the haemoglobin by endocytic vesicles. Ingestion of haemoglobin provides a source of amino-acids for the parasites and promotes their growth within the erythrocyte (Egan 2008).

Furthermore, malaria acute phase is associated with transient changes in lipid metabolism and derangement of serum lipid profile, occurring in both complicated and non-complicated malaria cases (Sibmooh et al. 2004; Visser et al. 2013). Similarly, reports have indicated uric acid

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(UA) as an additional parasite-derived factor that may contribute to malaria pathogenesis (Lopera-Mesa et al. 2012). Malaria parasites depend on exogenous hypoxanthine and xanthine as sources of purine since they cannot synthesise purine de novo. Once parasitized RBCs are ruptured, hypoxanthine is released into the extracellular medium and it is then metabolized by xanthine oxidase into UA (Guermonprez et al. 2013).

Plasmodium spp induce production of reactive oxygen species in infected erythrocyte, resulting in conversion of heme to hematin, the pigment that characterizes the feverish condition in malaria (Esan 2015). Meanwhile, erythrocytes rely on glucose-6-phosphate dehydrogenase (G6PD) for protection against oxidative damage and proper functioning (Howes et al. 2013). However, malaria parasites also compete with host for G6PD as they cannot thrive well in a G6PD deficient cell (Tishkoff et al. 2001).

Resistance of *Plasmodium* spp to the currently available anti-malaria drugs is one of the major reasons for malaria control failure (Dondorp et al. 2010). This necessitates searching for novel source of effective and efficient anti-malaria drugs, with little adverse effect at physiological doses. Sodium acetate has been previously shown to inhibit histone deacetylation and cell proliferation (Soliman and Rosenberger 2011; Marques et al. 2013). Our previous work has also shown anti-plasmodial activity of sodium acetate (Abdulkareem et al. 2018). In this study, we therefore aimed to investigate the effect of sodium acetate on serum activity of G6PD in *Plasmodium berghei*-infected mice.

Materials and methods

Experimental animals

For this study, thirty-six male Swiss albino mice (18–23 g), procured from Animal house holding, Biochemistry department, University of Ilorin, Ilorin, Kwara State, were used. The mice were transferred to the Animal house, Department of Zoology, University of Ilorin and were allowed to acclimatize for 14 days under standard laboratory conditions, with access to food and water ad-libitum. They were handled in accordance with the rules and regulations of the Animals Care and Use Committee (ACUC) and the Institutional Ethical Review Board of University of Ilorin.

Inoculation of parasites

The animals were inoculated intraperitoneally with an aliquot of 0.2 ml of a chloroquine-sensitive *P. berghei* (ANKA strain) inoculum (1×10^7 infected erythrocytes),

obtained from National institute of medical research (NIMR), Lagos, Nigeria.

Animal grouping and treatment

The acclimatized mice were randomly divided into six groups of six mice each. Groups A (uninfected) and B (infected untreated): received distilled water. Group C (chloroquine): infected and treated with 20 mg/kg body weight (b.w) chloroquine. Groups D, E and F (sodium acetate): infected and treated with 25 mg/kg, 50 mg/kg and 100 mg/kg b.w sodium acetate, respectively. All treatments were administered orally for 4 days. Body weight, food intake and water consumption rate were monitored throughout the treatment period.

Estimation of parasitaemia and percentage parasite inhibition

For parasite load estimation, blood was obtained from the caudal tip of the animals on the first day of treatment (Day 0), smeared in a clean glass slide and stained with Giemsa. The procedure was repeated on Days 2 and 4. The parasitaemia and percentage (%) parasite inhibition were then determined as previously described (Adetutu et al. 2016).

Sample preparation

At the end of the experiment, four mice from each group were sacrificed by cervical dislocation and blood was collected through cardiac puncture into plain bottle and centrifuged at 3000 revolution per minute for 5 minutes. Serum was stored frozen until needed for biochemical assays. Heart, kidneys and liver were excised, blotted and weighed immediately.

Biochemical assays

Fasting serum levels of G6PD, total cholesterol (TC) and triglyceride (TG) were estimated by standardized enzymatic colorimetric methods using assay kit obtained from Fortress Diagnostics Ltd. (Antrim, United Kingdom). High density lipoprotein-cholesterol (HDL-C) was measured by enzymatic clearance assay (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan), while low-density lipoprotein-cholesterol (LDL-C) was estimated using modified Friedewald's formula (Friedewald et al. 1972). TC/HDL-C and TG/HDL-C ratios were estimated as markers of atherogenic lipid indices. Method of Tietz (1994), as outlined in Randox kits, UK, was employed for the estimation of serum uric acid.

Statistical analysis

Data were presented as mean $\pm$ standard error of mean (S.E.M). One-way analysis of variance (ANOVA) followed by Bonferroni post hoc test was performed, using PRISM 5.0 (GraphPad Software, USA). Values were considered significant at $p < 0.05$.

Results

Anti-plasmodial test

Table 1 shows the effect of sodium acetate on parasitaemia, while Fig. 1 reveals the inhibitory effect of sodium acetate on *P. berghei* growth. Daily increase ($p < 0.05$) in parasitaemia was recorded in the infected-untreated group (Table 1). Meanwhile, treatments with chloroquine and sodium acetate (at all tested doses) significantly reduced ($p < 0.05$) parasite density. Sodium acetate at doses 50 and 100 mg/kg reduced parasite density than chloroquine, while the decrease was lesser in 25 mg/kg sodium acetate than chloroquine. Anti-plasmodial activity of sodium acetate was dose-dependent (Fig. 1). The highest (77.62%) and lowest (46.68%) percentage parasite inhibitions were observed in groups treated with 100 mg/kg and 25 mg/kg sodium acetate, respectively.

Physiological parameters

There was a decrease ($p < 0.05$) in daily food intake in infected untreated group when compared with uninfected group, whereas water consumption rate was similar for all the groups (Table 2). Also, heart, kidney and liver weights were not affected across the groups (Table 2). Significant increase in daily body weight was observed in uninfected control (Table 3). In contrast, there was no improvement in body weight of the infected untreated mice, while

treatment with chloroquine and 100 mg/kg sodium acetate improved body weight.

Lipid profile and atherogenic lipid indices

As shown in Table 4, *Plasmodium berghei* has no significant effect ($p > 0.05$) on lipid profile as well as TC/HDL-c. However, Chloroquine treatment significantly elevated ($p < 0.05$) atherogenic lipid ratio (TG/HDL-c ratios), while sodium acetate did not show significant effect on TG/HDL-c (Fig. 2).

Circulating uric acid and glucose-6-phosphate dehydrogenase

There was a slight increase ($p > 0.05$) in circulating level of uric acid in *P. berghei*-infected untreated group (Fig. 3). Meanwhile, chloroquine and sodium acetate treatments lowered serum uric acid level. In contrast, serum activity of glucose-6-phosphate dehydrogenase (G6PD) significantly decreased ($p < 0.05$) in *P. berghei*-infected untreated mice when compared with uninfected control (Fig. 4). After 4-day treatment, both chloroquine and sodium acetate improved the activity of G6PD.

Discussion

This study investigated the effect sodium acetate on serum glucose-6-phosphate dehydrogenase (G6PD) activity in *P. berghei*-infected mice. Our findings showed that, *P. berghei* infection had no effect on organ weights as well as water intake but reduced food intake and thus, hindered body growth. Our results also demonstrated that, infection with *P. berghei* had no effect on lipid profile but slightly elevated SUA and significantly reduced serum G6PD activity. We also demonstrated that, treatment with sodium acetate significantly inhibited parasite growth and improved food intake as well as body weight. Furthermore,

Table 1 Effect of sodium acetate on parasitaemia (parasite/ μ L of blood) in *Plasmodium berghei*-infected mice

Group	Day 0	Day 2	Day 4
Uninfected	0.00	0.00	0.00
Infected untreated	12.23 $\pm$ 3.57	15.63 $\pm$ 3.13	41.58 $\pm$ 1.31*
Chloroquine (20 mg/kg)	18.45 $\pm$ 3.27	9.70 $\pm$ 2.79	7.06 $\pm$ 1.82*
Acetate (25 mg/kg)	18.01 $\pm$ 6.66	13.24 $\pm$ 3.47	9.60 $\pm$ 2.96
Acetate (50 mg/kg)	25.76 $\pm$ 0.23	10.59 $\pm$ 3.68*	8.47 $\pm$ 2.23*
Acetate (100 mg)	20.11 $\pm$ 1.71	13.90 $\pm$ 3.87	4.50 $\pm$ 1.05*

Chloroquine and sodium acetate progressively reduced parasitaemia. Values were expressed as mean $\pm$ S.E.M of 4 mice per group. * $p < 0.05$ versus Day 0

Fig. 1 Inhibitory effect of sodium acetate on percentage parasite inhibitory effect of chloroquine (CQ) and sodium acetate (Act) on *Plasmodium berghei* growth in mice. There was a progressive parasite growth in infected untreated group, whereas, CQ and Act significantly inhibited parasite growth, on Day 4 post-treatment. Values were expressed as mean $\pm$ S.E.M of 4 mice per group

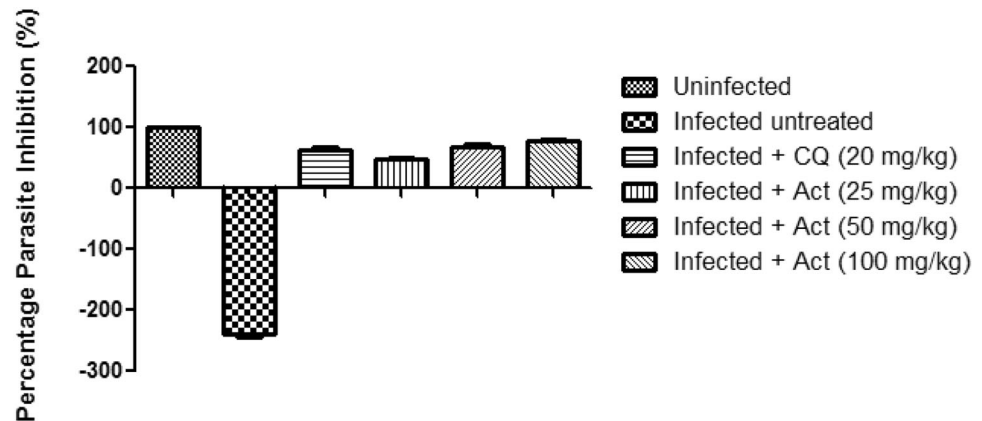


Table 2 Effect of chloroquine and sodium acetate on food consumption, water intake and organs weight in *Plasmodium berghei*-infected mice

Parameters (g)	Uninfected	Infected untreated	Chloroquine (20 mg/kg)	Acetate (25 mg/kg)	Acetate (50 mg/kg)	Acetate (100 mg/kg)
Food intake	33.28 $\pm$ 1.02	18.38 $\pm$ 0.45*	26.38 $\pm$ 0.68	33.28 $\pm$ 0.69	25.12 $\pm$ 0.75	27.08 $\pm$ 0.59
Water intake	26.67 $\pm$ 0.79	25.67 $\pm$ 0.68	20.89 $\pm$ 0.88	38.78 $\pm$ 0.99	33.44 $\pm$ 0.91	28.44 $\pm$ 0.81
Heart weight	0.10 $\pm$ 0.04	0.10 $\pm$ 0.01	0.10 $\pm$ 0.00	0.11 $\pm$ 0.01	0.11 $\pm$ 0.01	0.11 $\pm$ 0.00
Kidney weight	0.14 $\pm$ 0.01	0.14 $\pm$ 0.01	0.14 $\pm$ 0.01	0.15 $\pm$ 0.02	0.15 $\pm$ 0.02	0.15 $\pm$ 0.01
Liver weight	0.93 $\pm$ 0.13	1.35 $\pm$ 0.18	1.05 $\pm$ 0.03	1.25 $\pm$ 0.23	1.48 $\pm$ 0.10	1.39 $\pm$ 0.09

P. berghei infection resulted in reduced daily food intake, while both chloroquine and sodium acetate improved food intake. Daily water intake and organs weight remained similar ($p > 0.05$) for all the groups. Values were expressed as mean $\pm$ S.E.M of 4 mice per group. * $p < 0.05$ versus uninfected

Table 3 Effect of chloroquine and sodium acetate on daily body weight in *Plasmodium berghei*-infected mice

Groups	Body weight (g)		
	Day 0	Day 2	Day 4
Uninfected	19.33 $\pm$ 0.37	21.70 $\pm$ 0.21*	25.03 $\pm$ 0.29*
Infected untreated	19.51 $\pm$ 0.4423	18.44 $\pm$ 1.59	17.09 $\pm$ 1.63
Chloroquine (20 mg/kg)	20.70 $\pm$ 0.16	22.64 $\pm$ 0.26*	24.75 $\pm$ 0.37*
Acetate (25 mg/kg)	21.51 $\pm$ 2.02	20.05 $\pm$ 2.28	17.32 $\pm$ 1.88
Acetate (50 mg/kg)	20.07 $\pm$ 0.72	21.10 $\pm$ 1.21	20.97 $\pm$ 0.14
Acetate (100 mg/kg)	20.96 $\pm$ 0.27	23.83 $\pm$ 0.70*	24.80 $\pm$ 0.96*

Growth (in term of body weight) was hindered by *P. berghei*, whereas, chloroquine and 100 mg/kg sodium acetate progressively improved body weight. Values were expressed as mean $\pm$ S.E.M of 4 mice per group. * $p < 0.05$ versus Day 0

we showed that sodium acetate relatively lowered SUA and significantly improved blood activity of G6PD. The ameliorative effects of sodium acetate on the physiological and biochemical alterations in *P. berghei* infection compared favourably with chloroquine.

The inhibitory effect of sodium acetate on parasite growth confirms our earlier report on anti-plasmodial activity of the compound (Abdulkareem et al. 2018). This present study showed that sodium acetate had a better curative effect on *P. berghei* infection (at doses 50 and

100 mg/kg) than chloroquine (Table 1 and Fig. 1), suggesting that the compound may be a better alternative source of anti-malaria drugs. More so, increase in food intake as well as body weight upon treatment with sodium acetate (100 mg/kg) suggests the therapeutic value of the compound in correcting under-nutrition and weight loss that are often associated with malaria (Alexandre et al. 2015).

Reports on effect of malaria on lipid profile are conflicting (Krishna et al. 2009; Dias et al. 2016; Hamid et al.

Table 4 Effect of chloroquine and sodium acetate on lipid profile in *Plasmodium berghei*-infected mice

Parameters (mg/dL)	Uninfected	Infected untreated	Chloroquine (20 mg/kg)	Acetate (25 mg/kg)	Acetate (50 mg/kg)	Acetate (100 mg/kg)
HDL-C	87.61 ± 16.58	55.21 ± 0.68	62.47 ± 2.64	75.30 ± 11.88	55.21 ± 1.05	57.14 ± 0.68
LDL-C	208.26 ± 54.68	170.10 ± 6.25	235.4 ± 32.23	254.35 ± 29.61	145.60 ± 7.95	208.59 ± 28.64
TC	297.20 ± 16.95	207.15 ± 8.44	290.76 ± 27.06	216.80 ± 22.53	171.4 ± 2.69	259.96 ± 12.02
TG	185.8 ± 17.23	157.7 ± 3.74	203.8 ± 11.49	153.0 ± 5.06	142.3 ± 1.29	174.2 ± 6.54

P. berghei infection showed no significant effect ($p > 0.05$) on serum lipid profile at the end of the study. Values were expressed as mean ± S.E.M of 4 mice per group

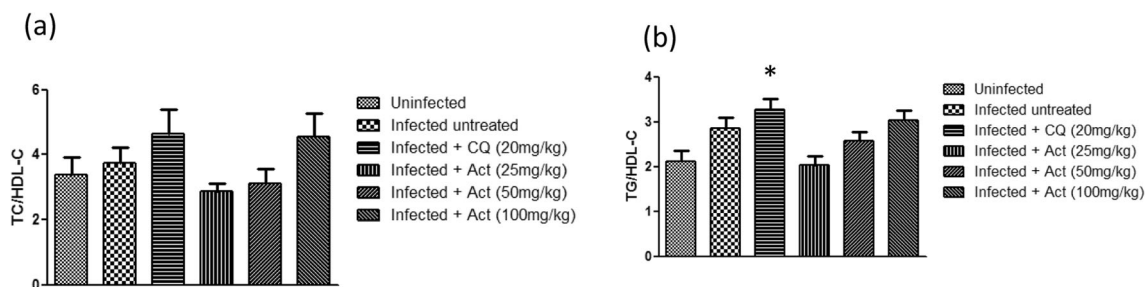
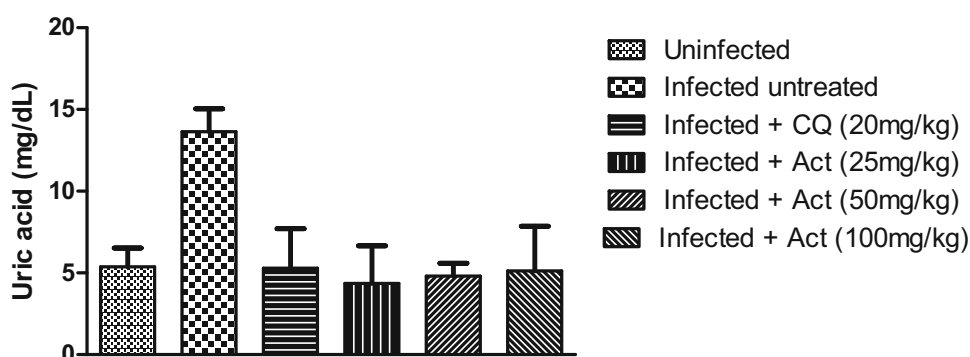


Fig. 2 Effect of chloroquine (CQ) and sodium acetate (Act) on atherogenic lipid indices (a & b) in *Plasmodium berghei*-infected mice. Both Act and CQ showed no significant effect on TC/HDL-c. However, CQ treatment significantly elevated atherogenic lipid ratio

(TG/HDL-C), whereas, Act did not significantly alter TG/HDL-C ratio. Values were expressed as mean ± SEM * $p < 0.05$ versus uninfected; $n = 4$

Fig. 3 Effect of chloroquine (CQ) and sodium acetate (Act) on serum uric acid (SUA) in *Plasmodium berghei*-infected mice. *P. berghei* infection slightly elevated SUA ($p > 0.05$), meanwhile, CQ and Act reduced SUA ($p > 0.05$). Values were expressed as mean ± S.E.M of 4 mice per group



2017; Vieira and Rivera 2017). However, results of this study on lipid profile are in consistent with our previous finding (Abdulkareem et al. 2018). Atherogenic dyslipidaemia, particularly TG/HDL-C ratio, is a useful and effective predictor of atherosclerotic cardiovascular disease (Musso et al. 2011). Thus, significant increase in TG/HDL-C observed in chloroquine treated-group may indicate that, chloroquine treatment, especially at exceeding dose, can lead to cardiometabolic disorder as previously suggested (Hussien 2007). Previous studies (Orengo et al. 2009; Musso et al. 2011) have reported uric acid (UA) as an additional parasite-derived factor that contributes to malaria pathogenesis, suggesting serum level of UA as a useful biomarker for severe malarial infection. In this

study, *P. berghei* slightly elevated serum level of UA. The mechanism of this elevation is not clear. However, it has been previously documented that dissolution of parasite-derived UA precipitates, the conversion of parasite-accumulated hypoxanthine and xanthine to UA by plasma xanthine oxidase, and the hemolysis of both parasitized and non-parasitized RBCs may be responsible for elevated serum UA in malaria (Lopera-Mesa et al. 2012).

Our present study showed that *P. berghei* infection reduced serum activity of G6PD. G6PD is a cytosolic enzyme that is necessary for the maintenance of redox potential, integrity, function and survival of RBCs, deficiency of which may result in intravascular haemolysis and haemoglobin degradation (Dessi et al. 1992).

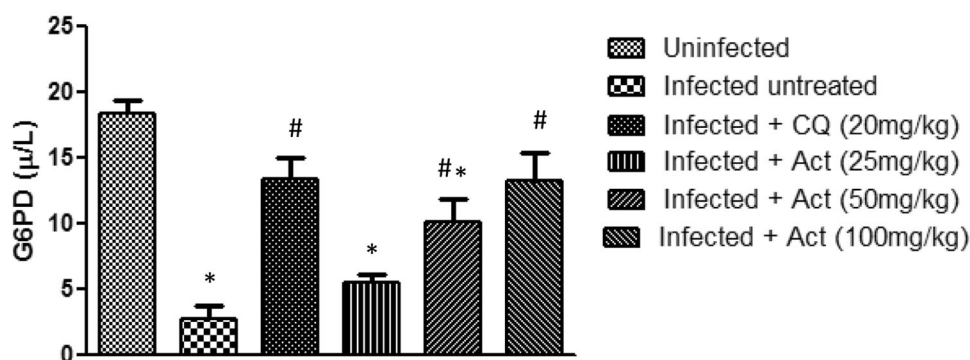


Fig. 4 effect of chloroquine (CQ) and sodium acetate (Act) on serum activity of G6PD in *Plasmodium berghei*-infected mice. At the end of the experiment, *P. berghei*-infected untreated mice showed reduced serum G6PD activity, while CQ and Act (50 and 100 mg/kg b.w)

improved its activity. Values were expressed as mean $\pm$ S.E.M of 4 mice per group. * $p < 0.05$ versus uninfected; # $p < 0.05$ versus infected untreated

Coincidentally, hyperuricaemia in malaria patients has been suggested to result from intravascular haemolysis and haemoglobin degradation (Hoffbrand and Moss 2016). Although not demonstrated, elevated SUA observed in infected untreated group of this study may in part be due to the reduced level of G6PD. There is an existing evidence that decrease in activity of G6PD can lead to cardiometabolic diseases (Hecker et al. 2012). Meanwhile, previous studies have reported the incidence of cardiometabolic diseases in malaria patients (Janka et al. 2010; Ahmad et al. 2013). Thus, our result which showed decrease in serum G6PD activity in infected untreated mice may suggest an association of malaria with cardiometabolic disorders which however, requires further investigations to proof. In concurrence with our previous studies (Usman et al. 2018; Olatunji et al. 2018), the present study showed that, treatment with sodium acetate, similar to chloroquine, significantly improved serum G6PD activity.

Conclusion

This study suggested that sodium acetate may be a novel source of anti-malaria drug which can efficiently attenuate malaria-related anorexia, weight loss and cardiovascular disorders. However, further studies are required to delineate its modes of actions.

Author contributions OLA and AOA: Conceived and designed the work that led to the submission, AOA, BOA, AAL and AOC: were responsible for the care of animals, collection and collation of data and analysis of data, AOA: interpreted the results and drafted manuscript, OLA and USU: supervised the study and edited the final manuscript.

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Compliance with ethical standards

Conflict of interest All authors of this manuscript declare that they have no conflict of interest related to the content of this manuscript.

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