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Full Length Research Article

Ethanol Extract of *Camellia sinensis* Elicited Hypoglycemic but Lacked Antimalarial Properties in *Plasmodium berghei*-Infected Diabetic Mice

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Summary: The *in vivo* antimalarial and antidiabetic potential of *Camellia sinensis* (ECS) extract in alloxan-induced diabetic and *Plasmodium berghei*-infected mice were investigated. Eighty-four BALB/c mice divided into sets 1 & 2 infected with *P. berghei* and 2 & 3 injected with alloxan received either distilled water, ECS (300mg/kg), Chloroquine (CQ-10mg/kg) or Metformin (250mg/kg). Results showed significant increases ($p<0.05$) in percentage parasitaemia of *P. berghei*-infected mice treated with ECS and *P. berghei*-diabetic mice. Furthermore, ECS significantly decreased ($p<0.05$) blood glucose and PCV in diabetic and *P. berghei*-diabetic mice. *ECS* regenerated pancreatic islet cells in *P. berghei*-infected-diabetes but lacked appreciable antimalarial activity.

Keywords: *antimalarial activity, hypoglycemic activity, ethanolic extract of Camellia sinensis, Plasmodium berghei, mice*

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INTRODUCTION

The high incidence and associated detrimental effects of diabetes mellitus has been a major medical challenge; it results to the poor physical and psychological state as well as the attendant morbid condition in diabetic patients (Moodley *et al.*, 2015). WHO reported the increased number of diabetics in double-fold in the past few years with 9% of total population above 18 years suffering from this disease (Alwan, 2010). If there is no improvement, it is projected that by year 2030, the number of diabetic patients would be 552 million (Whiting *et al.*, 2011). In Nigeria, diabetes mellitus is the commonest endocrine disorder in medical practice and is the major cause of morbidity and mortality with grave personal, social and economic consequences (Kim *et al.*, 2009). Diabetes is a heterogenous disorder characterized primarily by impaired hormone secretion, fat, protein and carbohydrate metabolism due to insufficient amount of insulin production or reduced sensitivity of tissue to insulin (Pistrosch *et al.*, 2015). It is associated with secondary complications including hypertension, neuropathy, retinopathy, cardiomyopathy, atherosclerosis, stroke, coronary ischemia etc (Rutter and Nesto, 2011). The generation of reactive oxygen species through the pro-inflammatory cytokine pathways has been implicated in the exacerbation of the secondary complications of diabetes (Chow *et al.*, 2004). Several reports have further demonstrated reduction in antioxidant activities in diabetes condition with consequent progression into oxidative stress leading to diabetic complications (Lopes de Faria *et al.*, 2011).

Camellia sinensis has received much attention because of its beneficial health effects such as anti-oxidant, anti-carcinogenic (Rashidi *et al.*, 2017; Jayashree *et al.*, 2017), and antimicrobial activities (Nibir *et al.*, 2017). It also contains phytochemicals with neuro-protective activity (Bai *et al.*, 2017; Ben *et al.*, 2016). The anti-infection (Nibir *et al.*, 2017) and antiviral (Burkard *et al.*, 2017) potential of *Camellia sinensis* catechins have been documented (Burkard *et al.*, 2017). As a reno-protective agent, green tea ameliorates diabetes and the related-complications whereas its flavonoids inhibit angiogenesis in several diseased settings including diabetic retinopathy (Peixoto *et al.*, 2015). Also, hyperglycemia and diabetes complications are controlled by EGCG which lowers insulin level, and plasma glucose as well as liver and kidney weights (Sampath *et al.*, 2017). Re-sensitization of insulin-resistant muscle to insulin by EGCG was recently studied (Pournourmohammadi *et al.*, 2017). *Camellia sinensis* was also reported to have a protective effect on experimental pancreatitis and promotes insulin sensitivity (Nomura *et al.*, 2015).

Recently, *Camellia sinensis* extract and its individual catechins have shown antimalarial activity against asexual blood-stage parasites (Sannella *et al.*, 2007). In malaria endemic region like Nigeria, there are incidence of diabetic patients that were presented with malarial infection. The availability of glucose for cellular functions becomes a problem during malaria infection. However, there is dearth of information on the effects of *C. sinensis* in *Plasmodium berghei* infected diabetic mice especially this particular specie that was grown in Nigeria expected to have certain characteristics different from the imported ones resultant from factors including geographical location and period of harvest etc which may influence pharmacological properties. Therefore, the purpose of this study was to evaluate the effect of ethanol extract of *Camellia sinensis* in *Plasmodium berghei* infected diabetic mice.

MATERIALS AND METHODS

Animal maintenance: Male albino mice weighing 23-28g were obtained from Central Animal House of the University

of Ibadan. The animals were acclimatized for two weeks before commencing the experiment. The animals were divided into nine groups of 8-10 per cage and fed with clean water *ad libitum* under a 12-hour light/dark cycle.

Preparation of ethanol extract *of Camellia sinensis* (ECS): *Camellia sinensis* extract was prepared as described by (Babu *et al.,* 2002). Briefly, the leaves were obtained from Cocoa Research Institute of Nigeria, Ibadan, Oyo State, Nigeria. The leaves were air dried and powdered in a miller. The powdered tea was extracted with 95% ethanol (for a high recovery of catechin) for 2 days with constant marceration and filtered on a Whatman No 1 filter paper. The pooled tea solution was evaporated in vacuo below 45^0C to obtain a residue. The dried extracts were stored at 4^0C.

Antidiabetic activity: Diabetes was induced in male mice fasted for 24 hours by single intraperitonial injection of 200 mg/kg body weight of alloxan monohydrate dissolved in 0.01M sodium citrate buffer (pH 3.0) (Xi-Qun *et al.,* 2005). Blood glucose levels of mice were determined after 72h with AccuCheck glucometer and animals with blood glucose levels $\geq$200mg/dl were considered diabetic and used for the study (Elased *et al.,* 1996). The diabetic mice were divided into six groups (IV – IX) of ten mice each as follows; Group IV diabetic mice (untreated) were given distilled water, Group V and VI were given 300mg/kg body weight ECS and 250 mg/kg body weight metformin, respectively. Non fasting blood was collected daily from these mice throughout the treatment and a week post-treatment. All treatments were administered orally to the mice. The remaining 3 groups (VII–IX) of diabetic animals were inoculated with malarial parasites and received treatments as stated below under antimalarial activity.

Induction of parasites and antimalarial activity: Mice in groups I-III (Healthy, n=10) and VII-IX (diabetic, n=10) were innoculated with a chloroquine sensitive *Plasmodium berghei* (ANKA strain). After 72hrs post-infection, thin films were made, fixed with methanol and stained with 10% Giemsa stain and used to monitor the parasitemia daily using X100 magnification of a light microscope. Treatments commenced when about 10% parasitemia were established in the mice which took about 72 hours. Animals in groups I and VII were administered distilled water, groups II and VIII received 300mg/kg ECS while groups III and IX received chloroquine.

Blood collection: Blood samples were collected from the tail of the mice in order to determine percentage parasitemia, packed cell volume (PCV) and blood glucose level. Two mice were sacrificed before treatment, 24 hours after treatment and a week post-treatment in all the groups. The liver and pancreas of these animals were collected and stored in 10% formalin and later used for histopathological analyses.

Histopathological evaluation: Tissue samples from the liver and pancreas were trimmed, processed by paraffin wax sections of 4µm thickness cut, stained with haematoxylin and eosin for light microscopic examination. Photomicrographs of relevant stained sections were taken and documented.

Statistical Analysis: Data were analyzed using the GraphPad prism v6.0 (Graphpad software, San Diego, CA, U.S.A). P-values less than 0.05 were considered significantly different. All the values were expressed as mean ± standard deviation.

RESULTS

Figure 1A shows the effect of treatment with ECS and chloroquine in malaria infected mice. The parasite infected untreated group had their parasitaemia increased with days of infection until death while the parasite infected mice treated with the standard drug, chloroquine had a rapid decrease in parasitaemia in the course of treatment compared with ECS treatment that had no effect on parasitaemia. Percentage parasitaemia in infected untreated group was observed to increase significantly ($p< 0.05$) on days 4 to day 7 when compared with day 0. Conversely, in infected chloroquine treated group, it decreased significantly ($p<0.05$) on day 4 and had completely cleared by day 14. A significant increase ($p<0.05$) in percentage parasitemia was also observed in malaria – ECS (300mg/kg) treated mice on days 4,5,6,7 and 14 when compared with day 0. The same pattern was observed (Figure1B) in parasitised diabetic mice given the same treatment.

Table 1 shows that malaria infected diabetic animals untreated group had the least mean survival time while the malaria-infected chloroquine treated animals had the highest mean survival time. The mean survival time for malaria-infected -diabetic animals treated with *Camellia sinensis* extract was low and similar to that of malaria untreated group. Similar pattern was observed in untreated parasitized diabetic mice.

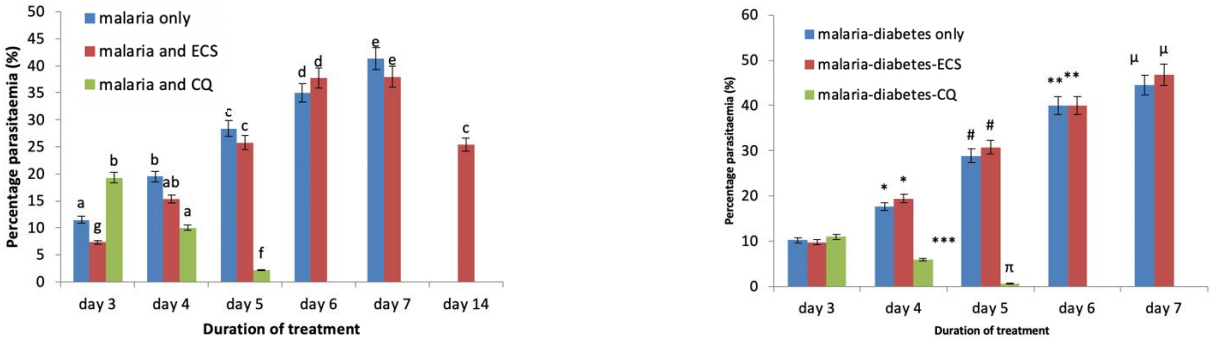

Figure 1
The effect of treatment with ECS on percentage parasitaemia in (A) mice infected with *P. berghei (B) P. berghei* infected diabetic mice. Values are expressed as Mean ± SD. Values with different letters, (*), (µ), (π), (#) and (**) are significantly different. ECS- Ethanol extract of *Camellia sinensis*, CQ- chloroquine

Table 1
The mean survival time of various treated groups

Group	Days (Mean±S.D)
Malaria untreated	9.9 ± 4.8
Malaria and *Camellia sinensis*	11.7 ± 2.0
Malaria and Chloroquine	31.4 ± 2.8*
Malaria-Diabetes untreated	7.8 ± 3.0
Malaria-Diabetes *Camellia sinensis*	9.1 ± 2.3
Malaria-Diabetes Chloroquine	30.5 ± 3.2*

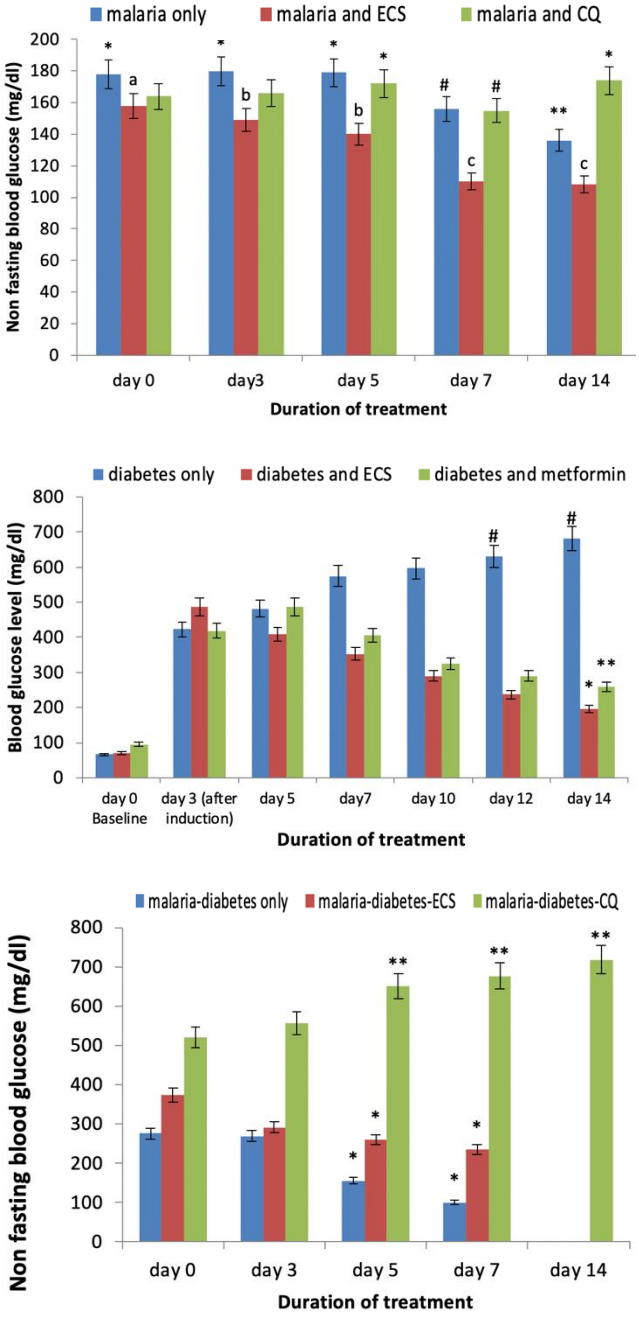

Figure 2
The effects of ECS on blood glucose level in (A) mice infected with *P. berghei*(B) diabetic mice (C) *P. berghei* infected diabetic mice
Values are expressed as Mean ± SD. Values with different letters, (*), (#) and (**) are significantly different. ECS- Ethanol extract of Camelliasinensis, CQ- chloroquine

Figures 2A and B show the effect of administration of ECS on blood glucose concentration in mice infected with malaria and diabetes. A significant decrease ($p<0.05$) in blood glucose level was observed in mice treated with ECS compared with infected untreated and chloroquine-treated groups. No changes were observed in the blood glucose level of mice treated with chloroquine and the untreated group at days 3, 4 and 5. However, the blood glucose level of the untreated group started to decrease steadily as the percentage parasitaemia increased. The blood glucose of mice treated with chloroquine increased progressively till day 14. Interestingly, blood glucose level in mice treated with the extract decreased relatively faster than that of the untreated group.

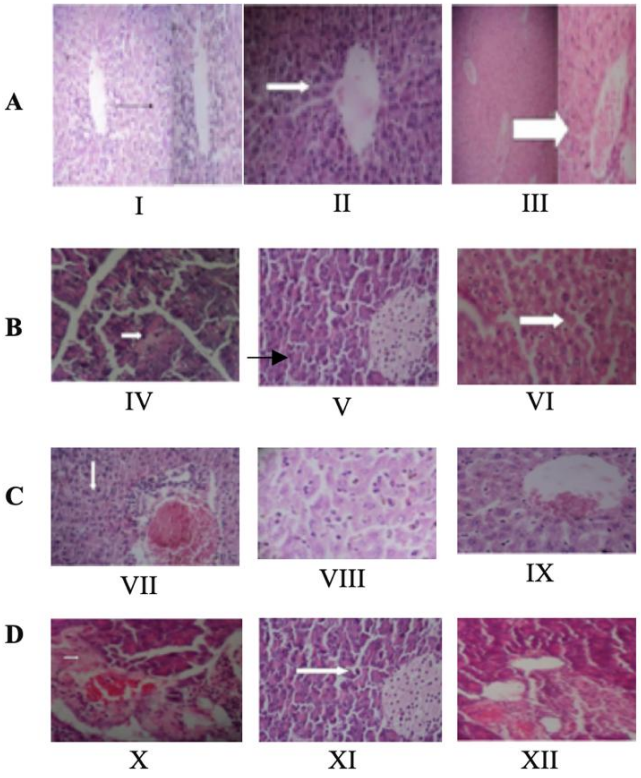

Plate 1
(A) Photomicrograph of the liver of P. bergheimice (I) without treatment (II) treated with 300mg/kg Camellia sinensis (III) treated with 10mg /kg chloroquine. I - shows sinusoidal dilation with perivascular mononuclear infiltration, centrilobular necrosis and kupfer cell hyperplasia with hemosiderosis.II-shows sinusoidal dilation with mononuclear cell infiltration.Perivascular, foci, kupfer cell hyperplasia with hemosiderosis.III-massive hepatic degeneration, mild perivascular mononuclear infiltration with Kupffer cell hyperplasia and mild hemosiderosis. X 100 Hematoxylin and eosin stain, (H&E).
(B) Photomicrograph of the pancreas of diabetic mice (IV) without treatment (V) treated with 300mg /kg Camellia sinensis, and (VI) treated with 250mg/kg metformin. IV- shows massive islet cell necrosis and degeneration. V-shows Mild islet cell necrosis and degeneration and VI-.Shows apparently normal islet cells.X 100 Hematoxylin and Eosin stain, (H&E).
(C) Photomicrograph of the liver ofP. berghei diabetic mice (VII) without treatment (VIII) treated with 300mg/kg Camellia sinensisand (IX) treated with 10mg/kg CQ. VII - shows kupffer cell hyperplasia with marked focal perivascular lymphocytic infiltration. VIII-shows sinusoidal dilation with perivascular mononuclear cell infiltration, centrilobular necrosis and kupffer cell hyperplasia with hemosiderosis.IX-shows sinusoidal dilation and kupffer cell hyperplasia with mild hemosiderosis. X 100 Hematoxylin and eosin stain, (H&E).
(D) Photomicrograph of the pancreas of P. berghei diabetic mice. VII without treatment, VIII treated with 300mg/kg Camellia sinensis and IX treated with 10mg /kg chloroquine. VII - shows massive islet cell necrosis and degeneration. VIII - shows mild islet cell necrosis and degeneration. IX - shows severe pancreatic islet necrosis. X 100 Hematoxylin and eosin stain, (H&E)

Figure 2C shows a significant decrease ($p<0.05$) in blood glucose in diabetic mice treated with ECS or metformin when compared to the untreated group. There was a significant decrease ($p<0.05$) in blood glucose level in untreated and extract treated groups when compared with chloroquine group. The blood glucose level in untreated mice decreased as the percentage parasitaemia increases. Chloroquine did not have effect on control of blood glucose level as there was a significant increase in blood glucose level in the chloroquine treatment group compared to that of the extract or metformin. Similarly, the blood glucose concentration of mice in the malaria infected diabetic ECS treated group decreased.

Table 2 shows the pattern of PCV changes in the *P. berghei* infected mice. The PCV decreased steadily in both untreated and ECS treated *P.berghei* infected mice. There was no significant difference ($p>0.05$) in PCV when these two groups were compared. PCV values were similar among all groups up till day 3. However, by days 7 and 14, PCV was significantly lower in ECS treated and untreated groups when compared with the chloroquine group. The pattern of PCV changes was similar in *P. berghei* infected diabetic mice (Table 3).

Table 2A: The packed cell volume (%) in *P. berghei* infected mice treated with ECS and chloroquine (CQ)

Days	Malaria untreated	Malaria and ECS	Malaria and CQ
Day 0	45.6 ± 2.7	44.3 ± 1.1	43.0 ± 4.6
Day 3	44.4 ± 3.0	46.3 ± 5.2	42.7 ± 3.7
Day 7	32.5 ± 8.0*	22.3 ± 1.1*	39.0 ± 5.7
Day 14	22.7 ± 2.3*	22.0 ± 1.0*	41.0 ± 7.8

Values are Mean ± SD. *significantly different from control. ECS – Extracts of *Camellia sinensis*

Table 2B: The packed cell volume (%) in diabetic mice treated with ECS and metformin

Days	Diabetes untreated	Diabetes and ECS	Diabetes and metformin
Day 0	45.4 ± 3.4	48.6 ± 2.9	45.3 ± 4.6
Day 3	45.6 ± 3.6	46.1 ± 3.0	46.6 ± 2.5
Day 7	44.1 ± 2.6	46.6 ± 2.4	44.9 ± 4.0
Day 10	43.9 ± 2.9	44.4 ± 5.5	48.0 ± 2.0
Day 14	42.1 ± 2.0	46.1 ± 3.3	41.4 ± 6.8

The PCV was not significantly affected in the diabetic mice by non-treatment or treatment with ECS or metformin from day 0 to 14

Table 2C : The packed cell volume of malaria infected diabetic mice treated with ECS or chloroquine

Day s	Malaria – Diabetes untreated	Malaria – Diabetes and ECS	Malaria – Diabetes and CQ
Day 0	45.4 ± 5.1	47.7 ± 4.4	44.6 ± 3.5
Day 3	39.6 ± 1.1	45.4 ± 3.5	40.0 ± 3.3
Day 7	23.4 ± 9.3	35.1 ± 4.7	40.0 ± 3.5
Day 14*	-	-	44.2 ± 2.4

The PCV of malaria – diabetic untreated mice decreased steadily up to 7 days. The PCV of the ECS treated malaria and diabetic mice were significantly reduced when compared to the untreated mice while the PCV of the CQ-treated malaria-diabetic mice was not significantly affected up to day 14.

*All the mice in the malaria-diabetic untreated group and malaria-diabetes extract group had died by day 14

Table 3

The percentage chemo-suppression (%) by ECS in malarial-infected diabetic and malarial -infected only male mice.

Days	Mal + ECS (%)	Mal + CQ (%)	Mal + Diab + ECS (%)	Mal + Diab + CQ (%)
3	36.5	68	4	-8
4	22	49	-10	7
5	9	92	-7	98
6	-8	100	0.3	98
7	8	100	-5	100
14	33	100	-	100

DISCUSSION

Hypoglycemia is implicated in malarial infection; for instance, infection with the lethal murine parasite *P yoelii YM* or the nonlethal parasite *P chabaudi* induces severe hypoglycemia as a result of hyperparasitemia and hyperinsulinemia (Elased *et al.,* 1994). Moreover, injection of parasitized blood cells to mice induces hypoglycemia (Taylor *et al.,* 1992). Similarly, extracts are capable of synergizing with insulin in enhancing glucose uptake in adipocytes *in vitro* (Taylor *et al.,* 1992) and of inducing insulin secretion from isolated pancreatic islets (Elased *et al.,* 1996). The present study was used as a model to investigate the effects of ethanolic extract of *Camellia sinensis* (ECS) on parasitized diabetic mice by evaluating the blood glucose levels.

The present study reports the anti-diabetic effects of ECS in alloxan-induced diabetic mice. This study showed that 300mg/kg of the ECS was effective for the treatment of diabetes. It was observed that the blood glucose level of diabetic mice was steadily reduced when compared to that of untreated diabetic mice such that the treated mice became hypoglycemic (reference point $\geq$ 200mg/kg) by day 14. The reduction of blood glucose level by the standard drug (metformin) and ECS followed the same pattern. This finding corroborates the report of Sabu *et al.,* (2002) that oral administration of green tea polyphenols reduced the serum glucose tolerance in alloxan– induced diabetic rats and also increased the antioxidant potential in the rats. Wu *et al.* (2004) also reported rapid normalization of blood glucose level in diabetic rats by green tea extract, and suggested that green tea extract protected the β-cells against the streptozotocin toxicity by regenerating the damaged cells. The anti-diabetic effect of the water-soluble polysaccharide fraction has also been documented (Han *et al.,* 2011). Furthermore, Sun *et al.,* (2016) reported that green tea polyphenols inhibited salivary amylase, intestinal sucrase and α-glucosidase, suggesting that the inhibitory activity of catechins against carbohydrates digestibility may be responsible for its ability to reduce blood glucose levels in diabetic rats, and these mechanisms may be responsible for the anti-hyperglycemic effect of green tea

Furthermore, the significant decrease ($p<0.05$) in blood glucose level in *P.berghei* infected diabetic mice treated with ECS and untreated *P.berghei*infected diabetic group when compared with chloroquine treated group might be due to the regeneration of the islet cells seen after 24 hours post-treatment. As the blood glucose of the untreated *P.berghei* diabetic group reduced, the percentage

parasitemia increased implying that the parasites might be utilizing the glucose for its metabolism.

Malaria parasites do not store glycogen or other reserve polysaccharides at the intra-erythrocytic stage (Elased *et al.,* 1995). As a result, the growth and reproduction of *Plasmodia* depend on simple sugars (notably glucose). Olszewski and Llinas (2011) observed that *P. falciparum* and *P. vivax*-infected erythrocytes required addition of glucose for their maintenance *in vitro* and they detected only maltose as an adequate substitute for glucose. Similarly, Kirk *et al.,* (1996) noticed the severity of infection of *P. falciparum* was intensified by glucose uptake. In contrast, many reports have shown that normal erythrocytes used very little of the added metabolite, oxygen, glucose and several other sugars as well as glycerol *in vitro* (Olszewski and Llinas, 2011). Thus, the sudden increase in glucose consumption by erythrocytes infected with a malarial parasite is resulted from an alteration in the permeability barrier of the erythrocyte membranes since chicken, duckling and mouse erythrocytes demonstrated a low sugar uptake. Thus, the presence of the malaria parasite promotes sugar uptake in malaria-infected erythrocytes by changing the permeability characteristics of the host cell.

The reduction of the elevated blood glucose by green tea and its catechins was reported in both type 1 and type 2 diabetic animals (Sabu *et al.,* 2002; Thipubon *et al.,* 2015). Green tea was shown to enhance the basal and insulin-stimulated glucose uptake of rat adipocytes (Wu *et al.,* 2004). Epigallocatechin gallate (EGCG) inhibit intestinal glucose uptake by sodium-dependent glucose transporter SGLT1 (Waltner-Law *et al.,* 2002) and mimic insulin by decreasing the expression of genes that control gluconeogenesis (Thipubon *et al.,* 2015). The antihyperglycemic effect of green tea extract may be linked to the increased glucose uptake, inhibition of intestinal glucose transporter and repression of genes that control gluconeogenesis (Kobayashi *et al.,* 2000; Musial *et al.,*2020).

Observation from the present study indicated that graded doses of the ECS administered to parasitized mice in a pilot study carried out in our laboratory revealed that the extract does not have any effect on parasite clearance in mice. The data in Figure 1 showed that the parasite infected untreated group had their parasitaemia increased steadily with days of infection until death which was similar to the findings in the ECS treated mice group. The pattern of result was similar in alloxan diabetic mice infected with *P. berghei*. This result correlates with the report of (Thipubon *et al.,* 2015) that epicatechin did not inhibit the growth of *P. berghei* in mice when administered for 4 consecutive days but it is at variance with the findings of Sannella *et al.,* (2007) that gallated catechins, epicatechin gallate and epigallocatechin gallate inhibited *Plasmodium falciparum* (strains NF54, K1 and 3D7) growth, with IC_{50} values between 10 and 40µM *in vitro*. The less IC_{50} values in excess of 100–300µM of ungallatedcatechins revealed its less potency. Sannella *et al.,* (2007) could not determine a precise mechanism of antimalarial action for catechins, but established that anti-folate mechanism of action was unlikely.

The PCV of *P.berghei*infected mice treated with ECS like that of untreated *P.berghei* infected mice were significantly decreased ($p<0.05$) when compared with the chloroquine treated group (Table 2). Since the ECS does not have antimalarial property. It is not surprising that there was a similarity in the PCV values of malaria - untreated and ECS-treated mice as Plasmodium infection is known to induce anaemia. In the study with *P.berghei* diabetic mice, the PCV of the untreated and that of ECS-treated animals decreased significantly ($p<0.05$) when compared with chloroquine-treated mice. The rate of PCV reduction was significantly different for untreated *P.berghei* diabetic mice and that of ECS treated *P.berghei* diabetic mice (52% and 23%), respectively. Elased *et al.,* (1994) reported that malaria lowers the blood glucose in diabetic animals and diabetes exerts a partial control over parasitaemia, and consequently anaemia, probably via an activating effect on macrophages. The PCV of untreated diabetic mice and that of the ECS treated diabetic group was similar to that of the metformin treated group. This is probably because diabetes does not have direct effect on red cell lysis.

In conclusion, our findings indicated that ethanol extract of *Camellia sinensis* possesses hypoglycemic activity as documented by blood glucose lowering effects in alloxan-induced diabetic mice and *P.berghei* infected diabetic mice. It however does not seem to have anti-malaria activity as portrayed by its inability to attenuate the parasitaemia in *P.berghei* infected ECS treated and *P. berghei* infected, diabetic ECS treated.

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