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COMBINED ORAL CONTRACEPTIVE (ETHINYLESTRADIOL/ LEVONORGESTREL) ALLEVIATES LIPID AND LACTATE ALTERATIONS IN PLASMODIUM BERGHEI-INFECTED MICE

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Despite the common use of combined oral contraceptive (COC) as a childbirth control pill, there is no sufficient information on the effect of COC in malaria. Hence, we aimed at investigating the effect of COC on parasite growth and the associated risk of metabolic disorder in Plasmodium berghei-infected mice. Twenty female mice were randomly allotted into four groups (n= 5/group): uninfected, infected (inoculated with P. berghei), COC (1.0 µg ethinylestradiol and 5.0 µg levonorgestrel, p.o/day, without infection) and infected + COC. Percentage parasitaemia was recorded weekly. At the end of 21-day exposure, the mice were sacrificed, while blood and liver were collected for biochemical analyses. Our data showed progressive increase in parasitaemia in P. berghei-infected mice. Our findings also revealed that P. berghei infection did not affect serum levels of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and total cholesterol (TC). It, however, elevated serum malondialdehyde (MDA), serum and liver triglycerides and liver TC. Elevations of serum and liver free fatty acid and lactate were also observed in P. berghei-infected mice. However, COC treatment lowered MDA level and attenuated lipid and lactate alterations in P. berghei infection. This study, therefore, suggests that COC possesses anti-plasmodial potential to mitigate malaria-associated metabolic disturbances. Further animal and human studies are necessary to validate our findings.

***Keywords**: Plasmodium berghei; malaria; COC; metabolic; lipid*

INTRODUCTION

Despite decline in mortality due to malaria, malaria still remains the leading cause of parasitic death worldwide, constituting a major global burden[1]. World Health Organization (WHO) estimated that more than 400,000 lives were lost to malaria alone in 2018, majority of which occurred in Africa and Asia parts of the world[2]. Four major species of *Plasmodium* (*P. ovale, P. vivax, P. malariae* and *P. falciparum*) are known to cause malaria in human. Out of the four, *P. falciparum* is the most virulent and commonest species found in sub-Saharan Africa. Hence, malaria poses a serious public health threat to Sub-Saharan Africa, Nigeria inclusive[3]. The migratory sporozoites from infected mosquito during blood feeding marks the onset of malaria infection in human. In the liver, the parasite

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multiplies and forms numerous merozoites (pre-erythrocytic stage), before finally entering the erythrocytes where the merozoites rupture, forming trophozoites and eventually schizont (erythrocytic stage)[4]. During the erythrocytic stage of the *Plasmodium*, the growing parasite modifies the host erythrocytes structurally, biochemically and functionally, resulting in several pathological conditions[5].

Malaria pathology varies from mild to severe symptoms and depending largely on host-parasite interaction, the infection often proceeds to a complicated case especially when diagnosis and appropriate treatment are delayed[6&7]. Parasites may overwhelm the host protective apparatus, thus resulting in depletion of nutrients and signaling molecules which may lead to impaired lipid metabolism as well as metabolic acidosis[8&9]. Liver is the central organ that regulates lipid metabolism. Coincidentally, liver serves as an initial micro-habitat for *Plasmodium* before symptom is initiated, the consequence of which may be hepatic lipid accumulation and metabolic dysfunction[7].

Over 100 million young women currently use combined oral contraceptive (COC) as a birth control pill[10]. Interestingly, non-contraceptive properties of these pills are well documented. For instance, ameliorative effects of COC on dysmenorrhea, fibroid-related symptoms, acne, premenstrual dysphoric disorder and maternal mortality have been reported[11&12]. While studies on its adverse impact on the pathogenesis of cardiometabolic disorder remain unresolved[13,14], study from our group has shown that COC treatment improves insulin resistance in ovariectomized rats[15]. However, there is insufficient information on the role of COC in malaria. Although few studies have reported the relationship between malaria and the use of oral contraceptive (OC)[16,17], none of these studies reported the effects of OC on lipid and lactate metabolism in malaria. Besides, modifications in the currently used COC warrant re-evaluation of its effect in malaria. This study, therefore, investigated the effect of COC on parasite growth and associated risk of metabolic disorder in female mice infected with *P. berghei.*

MATERIAL AND METHODS

Experimental animals

Twenty female Swiss albino mice (weighing 17-27 g) procured from Animal house holding, Biochemistry Department, University of Ilorin, Ilorin, Kwara State, Nigeria were used in this study. The mice were transferred to the Animal house, Department of Zoology, University of Ilorin, Ilorin, Kwara State, Nigeria where they were maintained at a constant room temperature. The animals were kept in a well-ventilated plastic cage and provided with pelleted mice meal and water for two weeks' acclimatization. Animals were handled carefully and all procedures carried out on the animals were in accordance with the rules and regulations made by the Animals Care and Use Committee (ACUC) and in conformity to the guidelines of the Institutional Ethical Review Board.

Parasite inoculation and percentage parasitaemia

Plasmodium berghei (NK-65)-bearing mice were obtained from the Biochemistry Department of the university of Ilorin, Kwara State, Nigeria. Blood from the donor mice was collected and mixed with normal saline in the ratio 1:10, respectively. Mice were inoculated intraperitoneally with an aliquot of 0.2 ml of standard inoculum (1×10^7 infected erythrocytes), as previously reported[18]. After successful parasite growth by Week 0 (before commencement of treatment), thin blood smears were prepared from the tail of infected mice on microscopic slides and allowed to air dry. Slides were then fixed and stained with Giemsa for 30 mins. Subsequently, the slides were rinsed with running water and air-dried. The slides were later viewed under a light microscope (mag. × 100 obj.) with an immersion oil. Method of Adetutu *et al*, 2016[19] was used to estimate percentage parasitaemia.

Preparation of combined oral contraceptive (ethinylestradiol/levonorgestrel)

Microgynon Tablets (Venkat Pharma, India), containing a combination of ethinylestradiol and levonorgestrel pills were commercially obtained and prepared in distilled water at a combined dose of 1.0 and 5.0 µg/kg, respectively[15].

Experimental design

Mice were kept in well-ventilated plastic cages and provided with unlimited access to food and water *ad libitum*. They were acclimatized for 2 weeks and then randomly

selected and divided into 4 groups. Uninfected group (received only distilled water and were not inoculated with *P. berghei*), infected group (inoculated with *P. berghei* and given distilled water only), COC group (received a combination of 1.0 µg ethinylestradiol and 5.0 µg levonorgestrel per oral (p.o), without parasite inoculation), while infected + COC group were inoculated with *P. berghei*, followed by treatment with a combination of 1.0 µg ethinylestradiol and 5.0 µg levonorgestrel p.o). The treatments were administered daily, in each group and lasted for 21 days.

Sample preparation

At the end of the experiment by Day 21, 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 prepared and stored frozen until needed for biochemical assays. Liver was excised, cleansed of the associated connective tissue and mechanically homogenized in ice-cold 0.25M sucrose solution. The liver homogenates were further processed for biochemical analyses.

Biochemical assays

Lipid profile test

Serum and tissue levels of total cholesterol (TC) and triglyceride (TG) as well as serum high density lipoprotein-cholesterol (HDL-C) were estimated as previously reported[20]. Serum low density lipoprotein-cholesterol (LDL-C) and Low-density lipoprotein-cholesterol (VLDL-C) were estimated using modified Friedewald's formula[21].

Estimation of Free fatty acid, lactate and malondialdehyde

Tissue and serum levels of free fatty acid (FFA), lactate and malondialdehyde (MDA) were estimated by colorimetric method using assay kit obtained from Fortress Diagnostics, Ltd. (Antrim, United Kingdom), following manufacturer's instruction.

Statistical analysis

All data were analyzed and presented as mean ± SEM using GraphPad Prism software version 8.0 (GraphPad Software, USA). One-way analysis of variance (ANOVA), followed by Tukey post-hoc test, was used to compare the mean values among the groups. The significant difference was determined at 95% confidence level and $p< 0.05$, $p< 0.01$ and $p< 0.001$ were considered statistically significant.

RESULTS AND DISCUSSION

Results

Anti-plasmodial test

The pattern of percentage parasitaemia is presented in Fig. 1. Parasitaemia level increased progressively in infected group from Week 0 to Week 3, while combined oral contraceptive (COC) treatment significantly suppressed parasitaemia (34.4 % Week 0 vs 11.4 % Week 3) in infected mice.

Combined oral contraceptive (COC) treatment lowered lipid peroxidation in P. berghei-infected mice

Oxidative stress is implicated in the pathophysiology of malaria parasite; therefore, we assessed the serum level of malondialdehyde (MDA) in female *P. berghei*-infected mice, as a marker of lipid peroxidation. As compared with uninfected group, our data showed that *P. berghei* but not COC significantly increased ($p< 0.05$) serum MDA (Fig. 2), while treatment with COC lowered ($p < 0.01$) *P. berghei*-induced elevated MDA.

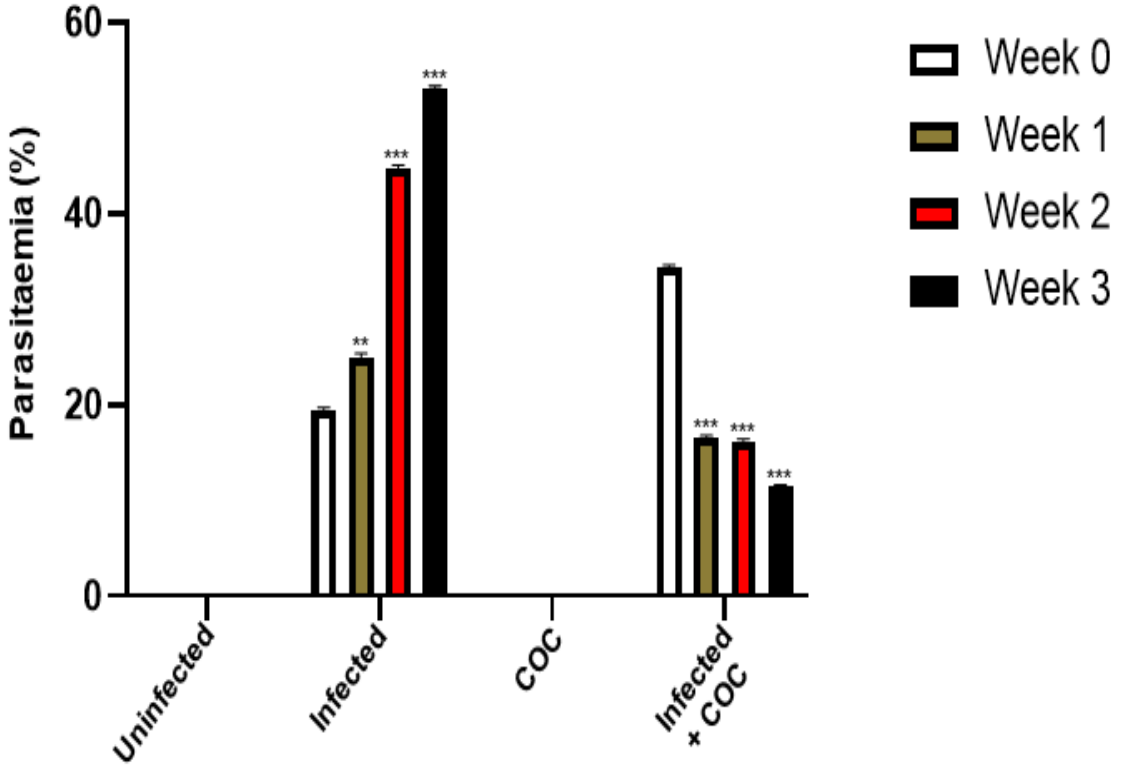

Fig. 1: Effect of combined oral contraceptive treatment on parasite growth. Data were expressed as mean ± SEM (n = 3). Data were analyzed by One-way analysis of variance (ANOVA) followed by the Tukey post hoc test. (**p < 0.001 vs Week 0 of the same group; ***p < 0.001 vs Week 0 of the same group).

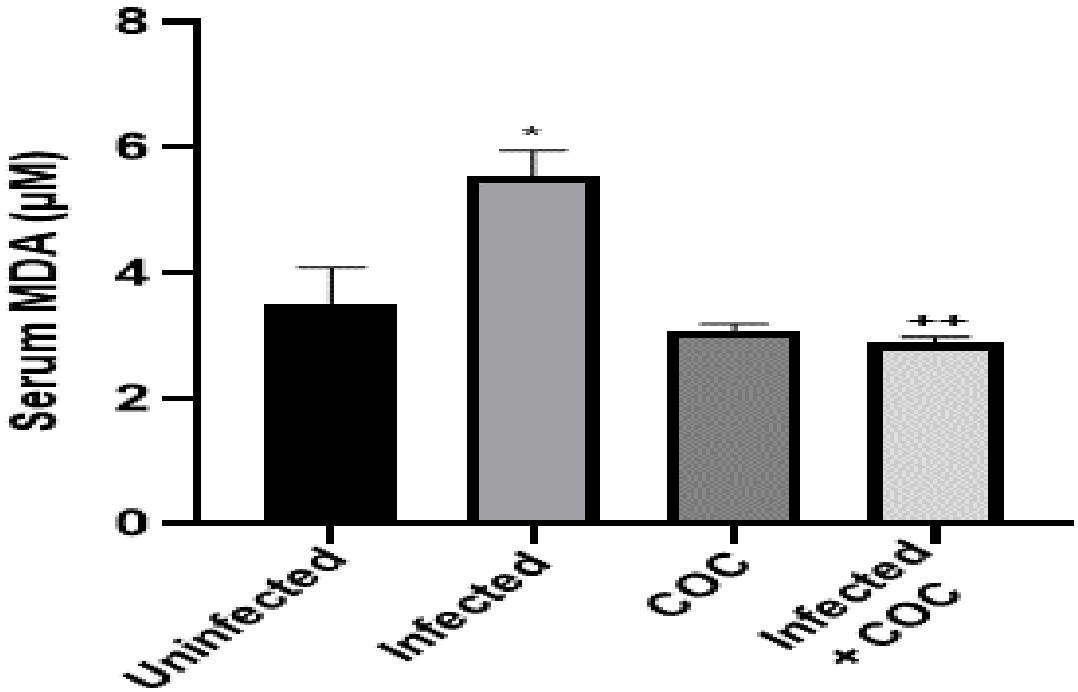

Fig.2: Effect of *Plasmodium berghei* and combined oral contraceptive (COC) on serum malondialdehyde (MDA) in female Albino mice. *P. berghei* but not COC elevated serum MDA (p < 0.05), whereas treatment with COC attenuated MDA in *P. berghei* infection. Data were expressed as mean ± SEM (n = 3). Data were analyzed by One-way analysis of variance (ANOVA) followed by the Tukey post hoc test. (*p < 0.05 vs uninfected; ++p < 0.01 vs infected).

Effect of combined oral contraceptive on lipid profile and hepatic lipid accumulation in P. berghei-infected mice

There was no significant change ($p > 0.05$) in serum levels of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) in both *P. berghei*-infected mice and COC treated mice (Table 1). However, infection with *P. berghei* significantly elevated serum triglycerides (TG) as well as liver TC ($p < 0.05$) and TG ($p < 0.01$), as compared with to uninfected mice (Fig. 3). In contrast, COC treatment reduced serum and liver levels of TG and decreased liver TC,when compared with uninfected group.

Table1: Effect of combined oral contraceptive (COC) on serum lipid profile in *Plasmodium berghei* infected mice.

Parameters (mg/dl)	Uninfected	Infected	COC only	infected + COC
HDL-C	8.56 ± 0.74	8.4.43 ± 0.61	10.63 ± 1.149	13.47 ± 1.838
LDL-C	44.94 ± 3.48	50.75 ± 1.32	47.90 ± 1.959	43.00 ± 1.774
Total Cholesterol	53.50 ± 3.31	59.19 ± 1.66	56.26 ± 3.408	56.47 ± 1.877
Triglycerides	56.80 ± 1.88	74.60 ± 3.71**	61.50 ± 2.69+	59.53 ± 1.35+
VLDL-c	12.52 ± 0.75	13.58 ± 0.92	11.58 ± 0.4262	12.27 ± 0.2748

There was no significant change in lipid prole across the group. Data were expressed as mean ± SEM (n = 3). Data were analyzed by One-way analysis of variance (ANOVA) followed by the Tukey post hoc test. (** $p <$ 0.01 vs uninfected; +$p < 0.05$ vs infected).

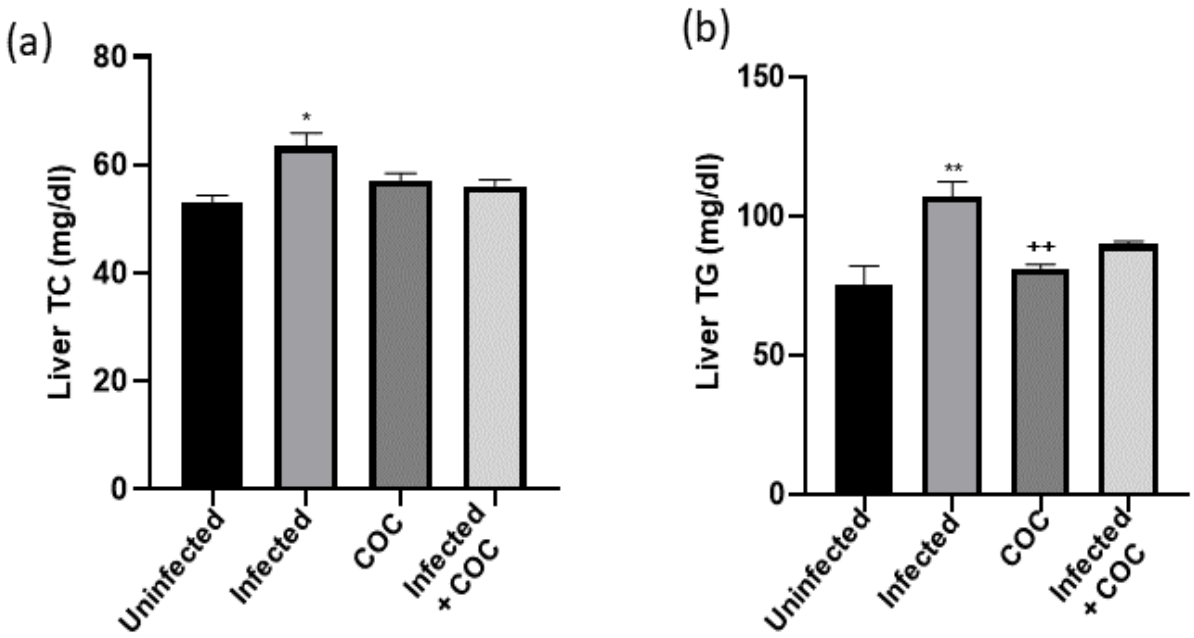

Fig. 3: Effect of *Plasmodium berghei* and COC on liver (a) total cholesterol (TC), (b) triglycerides (TG) in female Albino mice. *P. berghei* infection significantly increased liver TC and TG which were attenuated by COC treatment. Data were expressed as mean ± SEM (n = 3). Data were analyzed by One-way analysis of variance (ANOVA) followed by the Tukey post hoc test. (*$p < 0.05$ vs uninfected; ** $p <$ 0.01 vs uninfected; ++$p < 0.01$ vs infected).

Effect of combined oral contraceptive (COC) on serum and hepatic levels of lactate and free fatty acid (FFA) in P. berghei-infected mice

As shown in Fig. 4, there was a significantly increased level of FFA in the serum of mice infected with *P. berghei* ($p < 0.05$), while hepatic level of FFA was moderately elevated ($p > 0.05$), as compared with uninfected. Similarly, Fig. 5 of our data revealed that *P. berghei* increased serum and hepatic lactate levels ($p < 0.05$ and $p < 0.01$, respectively). However, COC treatment lowered serum FFA ($p < 0.05$) and alleviated *P. berghei*-induced lactate accumulation, with more effect in the liver ($p < 0.01$).

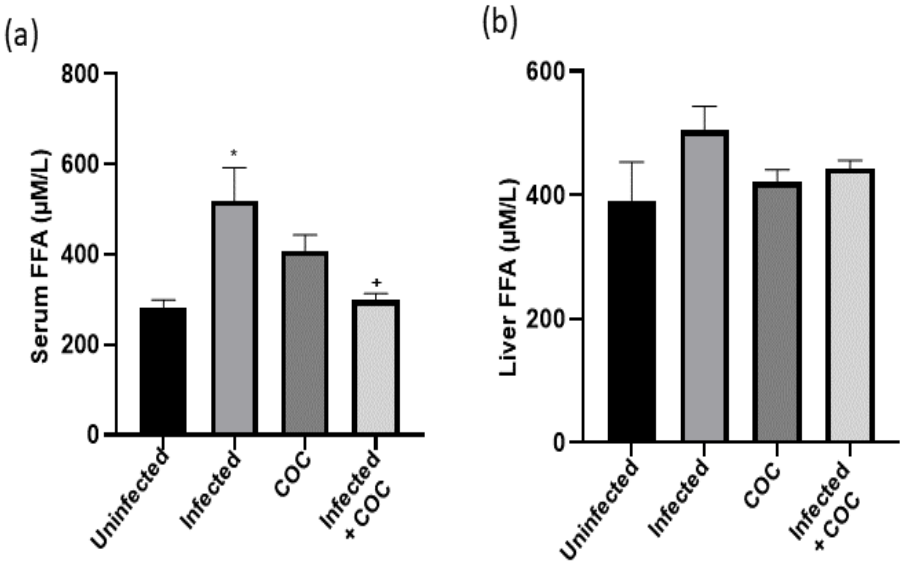

Fig.4: Effect of *Plasmodium berghei* and COC on (a) serum FFA, and (b) liver FFA in female Albino mice. *P. berghei* infection significantly increased serum FFA which was mitigated by COC treatment. Data were expressed as mean ± SEM (n = 3). Data were analyzed by One-way analysis of variance (ANOVA) followed by the Tukey post hoc test. (*$p < 0.05$ vs uninfected; +$p < 0.05$ vs infected).

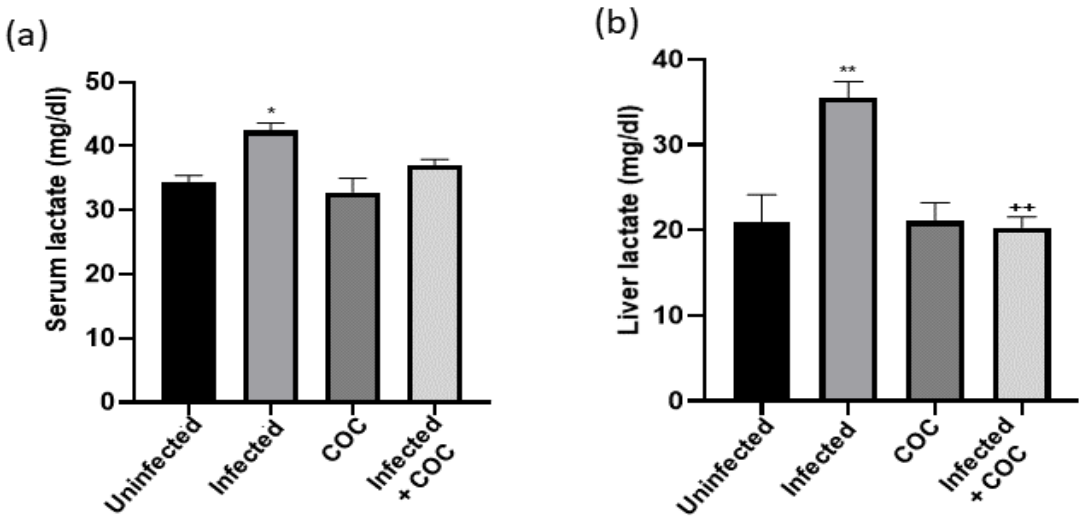

Fig.5: Effect of *Plasmodium berghei* and COC on (a) serum lactate, and (b) liver lactate in female Albino mice. *P. berghei* infection significantly increased liver lactate was attenuated by COC treatment. Data were expressed as mean ± SEM (n = 3). Data were analyzed by One-way analysis of variance (ANOVA) followed by the Tukey post hoc test. (** $p < 0.01$ vs uninfected; ++$p < 0.01$ vs infected).

Discussion

This study demonstrated that *P. berghei* infection elevated serum TG level, promotes lipid peroxidation (as evidenced by the increased serum level of MDA) and induces hyperlactatemia as well as hepatic lipid and lactate accumulation in female mice. Our findings also showed that combined oral contraceptive treatment (COC) suppresses parasite growth and attenuates parasite-induced lipid peroxidation, hyperlactatemia and hepatic lipid accumulations, an indicative of potential ameliorative effect of COC against malaria and associated metabolic disturbances. *P. berghei*, a murine parasite of Africa origin, shares similarities with human malaria parasites and represents a good animal model for malaria study[22]. This may therefore suggest the importance and relevance of our findings in human.

Our finding that revealed the lowering effect of COC on parasitaemia may be suggestive of anti-plasmodial effect of COC in women and that COC may probably prevent severity of infection. Oxidative stress is a common feature of many infections, including malaria and often mediates the inflammatory cytokines that may orchestrate malaria – associated pathology in the infected individuals[23]. We investigated the effect of *P. berghei* on MDA, an established marker of lipid peroxidation in severe malaria. Our results revealed an increased level of MDA at the end of 3-week *P. berghei* infection, which is in agreement with previous findings[7].

Alteration in lipid profile is another common characteristic of malaria with inconclusive findings[24]. This present study shows that *P. berghei* increased serum TG level. Although the mechanism is not clear, hypertriglyceridaemia has been suggested to be an indicator of severe malaria[25]. Therefore, our data that revealed lowering effect of COC on serum TG may be another indication that COC use lessens severity of malaria in women. We further provided evidence of total cholesterol and TG accumulations in liver homogenates of *P. berghei*-infected mice. This may be implicative of enhanced lipogenesis which may indicate involvement of metabolic complications in malaria[7]. Since excessive generation of oxidative stress promotes metabolic complications[23], the observed hepatic lipid accumulation may, in part, be due to *Plasmodium*-induced MDA formation.

FFA constitutes an important source of energy for several body tissues (including liver) and its serum level is physiologically maintained in healthy condition. However, increased lipolysis results in elevation of serum FFA, impairs insulin secretion and promotes the risk of metabolic disorder[26]. Hence, elevated level of serum FFA observed in *P. berghei* infection in this current study may indicate lipolysis and impaired insulin secretion, therefore, establishing a relationship between malaria and cardiometabolic risk. Interestingly, co-morbidity between malaria and diabetes has been previously reported, while diabetes incidence has increased with high fold in malaria endemic regions of Africa[27&28]. More so, elevated serum FFA can lead to oxidative stress and cause hypertriglyceridaemia with resulting lipotoxicity[29&30]. Therefore, elevated serum FFA reported in this study might have contributed to the generation of MDA and increased serum TG. We showed that COC treatment reduced serum FFA, decreased MDA and lowered hepatic lipid accumulation in female *P. berghei*-infected mice. These results, put together, may indicate the efficacy of COC to mitigate malaria-induced metabolic complications.

Hyperlactataemia is another metabolic impairment common to malaria, and together with lactic acidosis, serves as an important predictor of severe malaria[31]. In this study, we report elevated level of lactate in both serum and liver of *P. berghei*-infected mice which suggests respiratory distress and decrease in cardiac contractility in malaria infection. The etiology of *Plasmodium*-induced hyperlactataemia is not clear, however, it may be due to increased lactate production by the parasite[9] or impaired hepatic lactate clearance, as evidenced by the increased lactate level in the liver of *P. berghei*-infected mice. Elevated level of hepatic lactate in infected mice indicates intracellular acidosis which inhibits gluconeogenesis and enhances hepatic lactate synthesis. Hence, our finding suggests impaired gluconeogenesis in malaria. Administration of COC attenuated lactate levels, revealing potentiality of COC in preventing malaria severity and associated respiratory distress and lactic acidosis. Our findings on COC, put together, are in support of previous findings that reported no deleterious effect of oral contraceptives (OC) in malarial-infected human

and rhesus monkeys[16,17] but disagree with the report of Dutta *et al.* 1984[17], which shows slight cumulative parasite load in OC-treated monkeys. The difference may be related to the species of *Plasmodium* or type of contraceptive used.

In conclusion, we have shown, in this study, that combined oral contraceptive (COC) possesses anti-plasmodial property and mitigates malaria-associated metabolic disturbances in female mice with *P. berghei* infection. This study therefore implies that COC may be a relevant therapeutic agent in malaria treatment. Further studies are necessary to validate our findings and justify the relevance of COC use in malaria treatment.

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نشرة العلوم الصيدلية
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موانع الحمل الفموية المشتركة (إيثينيل إستراديول / ليفونورجيستريل) تخفف من تغيرات الدهون واللاكتات في الفئران المصابة بالبلازموديوم برجى

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على الرغم من الاستخدام الشائع لوسائل منع الحمل الفموية المشتركة (COC) كحبوب لمنع الحمل ، لا توجد معلومات كافية عن تأثير COC في الملاريا. ومن ثم ، فإننا نهدف إلى التحقيق في تأثير COC على نمو الطفيليات والمخاطر المرتبطة باضطراب التمثيل الغذائي في الفئران المصابة بـ البلازموديوم برجى (الطفيل المسبب للملاريا).

تم تقسيم عشرين أنثى فأر بشكل عشوائي إلى أربع مجموعات (ن = ٥ / مجموعة): مجموعة بدون عدوى ، مجموعة مصابة (تم عدوتها بالبلازموديوم برجى) ، مجموعة بدون عدوى تعطىCOC (١.٠ ميكروجرام من إيثينيل إستراديول و ٥.٠ ميكروجرام من الليفونورجستريل / يوم) ، و محموعة مصابة بالعدوى تعطى نفس الجرعة من.COC .

تم تسجيل نسبة التطفل في الدم أسبوعيا. في نهاية التعرض لمدة ٢١ يومًا ، تم التضحية بالفئران ، بينما تم جمع الدم والكبد لإجراء التحليلات الكيميائية الحيوية. أظهرت نتائجنا أن البلازموديوم برجى زاد تدريجياً من نسبة الطفيليات في الدم وارتفاع نسبة الدهون الثلاثية في الدم (TG) وكذلك نسبة المالونديالديهيد (MDA). وجد أيضًا أن البلازموديوم برجى يرفع نسبة الدهون الثلاثية في الكبد وكذلك الكوليسترول الكلي. علاوة على ذلك ، كانت هناك مستويات عالية من الأحماض الدهنية الحرة واللاكتات في كل من متجانس المصل والكبد للفئران المصابة. في المقابل ، خفض علاج COC مستوى المالونديالدهيد وخفف التغيرات في الدهون واللاكتات في عدوى البلازموديوم. لذلك ، تشير دراستنا إلى أن COC تمتلك خاصية مضادة للطفيل ويمكن أن تخفف من الاضطرابات الأيضية المرتبطة بالملاريا. هناك ضرورة للمزيد من الدراسات الحيوانية والبشرية للتحقق من صحة النتائج التي تم التوصل إليها.