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Research Article

Antiplasmodial and antipyretic activities of the *Monodora myristica* (Annonaceae) seeds

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Abstract

The seeds of *Monodora myristica* (Annonaceae) are pale brown, oblong-shaped, aromatic and are used in traditional medicine to treat malaria and fevers. Hence, this study aimed to evaluate the antiplasmodial and antipyretic activities of *M. myristica* seeds. The methanol extract of *M. myristica* (MME) was prepared and used for this study. The antiplasmodial effect was evaluated using *Plasmodium berghei* in both suppressive and curative models while the antipyretic effect was investigated using *P. berghei* and yeast-induced pyrexia in mice. The MME showed a significant dose-dependent reduction ($p < 0.01$ and $p < 0.001$) in parasitemia levels in both the suppressive and curative models. In the suppressive model, the 400 mg/kg MME group showed a comparable percentage of inhibition of parasitemia to that of artemether/lumefantrine (94.44% vs. 95.24%). In the curative model, the 400 mg/kg MME group showed a greater reduction than the reference drug (95.11% vs 94.57%). Additionally, MME (400 mg/kg) outperformed artemether/lumefantrine in *P. berghei*-induced pyrexia at Day 10 (5.23% Δ°C vs. 3.87% Δ°C). Notably, all MME doses significantly reduced the rectal temperature ($p < 0.001$) of mice in the yeast-induced model, with MME (400 mg/kg) showing superior temperature reduction than paracetamol at 4 h. *M. myristica* showed effective antiplasmodial effect against *P. berghei* in both the suppressive and curative models in infected mice. In addition, it effectively reduced rectal temperatures in *P. berghei*-induced and yeast-induced pyrexia. Further studies are underway to isolate and characterize the active molecules.

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1. Introduction

Malaria is a global health challenge and a leading cause of death in many countries, especially in sub-Saharan Africa [1]. It is caused by parasites from the *Plasmodium* genus, and spread via the bites of infected Anopheles mosquitoes. As of 2023, there were 263 million malaria cases and 597,000 recorded malaria deaths globally, with about 95% of these cases and deaths attributed to African regions [2]. More concerning is that about 76% of malaria-related deaths in the region occurred in children under the age of five [2]. Despite the progress made in the fight against malaria through the discovery of antimalarial agents, eradication efforts have been hindered due to the development of resistant strains, leading to reduced drug effectiveness and poor treatment outcomes [3]. Also, the limited accessibility and cost of conventional

antimalarials, especially artemisinin-based combination therapies, in low-resource settings may hinder drug adherence [4]. Therefore, there has been an increasing interest in alternative therapies using natural products and medicinal plants to overcome these limitations.

Monodora myristica (Annonaceae), also called the calabash nutmeg or African nutmeg, is a tropical tree that naturally grows in the tropical regions of Africa. The tree is medium to big in size, with a height of up to 35 m-[5]. The pale brown and oblong-shaped seeds are found inside the fruits of the plant. In traditional medicine, the seeds are used to treat various ailments, such as fever, malaria, anemia, and other parasitic infections [6]. Besides, studies have shown the pharmacological activities of *M. myristica,* including antioxidant, anti-inflammatory, hepatoprotective, and hypocholesterolemic effects [7–10].

Given the folkloric use of this plant in the treatment of malaria and fever, it is plausible to validate its use through scientific experiments. Since many malaria cases co-occur with fever [11], it is essential to find alternative treatment options with possible dual properties against malaria and fever. Therefore, this study was designed to investigate the antiplasmodial and antipyretic activities of the methanol seed extract of *M. myristica.*

2. Materials and methods

2.1. Collection of plant material and preparation of extract

Mature seeds of *Monodora myristica* were purchased from a local market in Agu Orba in Udenu L.G.A in Enugu State, Nigeria and authenticated by a taxonomist, Mr. Felix Nwafor, at the Department of Plant Science and Biotechnology, University of Nigeria, Nsukka. A voucher specimen was deposited in the departmental herbarium with the number UNN/13100. The seeds were washed, air-dried, and then pulverized. The powdered material was macerated in methanol for 72 h–with intermittent shaking. The mixture was filtered and concentrated under reduced pressure using a rotary evaporator at 40 °C to obtain a crude methanol extract (MME).

2.2. Phytochemical analysis

Preliminary phytochemical analysis of the crude methanol extract of *M. myristica* (MME) was performed using methods described by Harborne (1998) to determine the presence of alkaloids, flavonoids, saponins, tannins, terpenoids, cardiac glycosides, and steroids [12].

2.3. Experimental animals

A total of 75 adult albino Swiss mice of either sex weighing between 20-35 g were sourced from the animal house of the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka, Nigeria. The mice were maintained on a 12 h light/dark cycle and allowed to acclimatize for 2 weeks. They were fed with commercial rat feed and water *ad libitum.* The animal handling procedure was followed internationally accepted ethical standards [13]. The protocol was approved by the local ethics committee of our institution and was given the approval number FPSRA/UNN/25/0151

2.4. Acute toxicity test

The acute toxicity (LD_{50}) of MME was evaluated using Lorke's method [14]. The test was carried out in two phases using a total of 12 mice.

In the first phase, nine mice were randomly divided into three groups of three animals each and orally administered the extract at doses of 10, 100, and 1000 mg/kg body weight, respectively. The animals were observed for 24 h for signs of toxicity and mortality. In the second phase, based on the results of the first phase, three additional mice were separately administered higher doses of 1600, 2900, and 5000 mg/kg body weight to further determine the LD_{50} range.

All animals were carefully monitored for 24 h after dosing. Behavioral signs, such as tremors, salivation, convulsions, piloerection, respiratory distress, loss of appetite, and mortality, were recorded. The LD_{50} value was estimated as the geometric mean of the highest dose producing no mortality and the lowest dose causing death.

2.5. Evaluation of the antiplasmodial activity

2.5.1. Suppressive antiplasmodial activity (4-day test)

The suppressive antiplasmodial activity of MME was evaluated according to the methods described by Nworu *et al*. [15]. Twenty-five rats were each inoculated intraperitoneally with 0.2 mL of Plasmodium berghei-infected blood containing approximately 1×10^7 parasitized erythrocytes. The

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mice were then randomized into five groups (n = 5), where groups I—III received oral treatment doses of MME (100, 200, and 400 mg/kg) 2 h after infection for 4 days. Groups IV and V received oral standard 1:6 ratio of artemether/lumefantrine (4 mg/kg) and distilled water (10 mL/kg), respectively, for the same duration as the treatment group. Parasitemia levels were measured on Day 5 to calculate the percent suppression and then compared to the controls using the following formulae [15]:

$$\text{Parasitemia (\%)} = \frac{\text{Number of parasitized RBCs in fields}}{\text{Total number of RBCs in fields}} \times 100$$

$$\text{Suppression of parasitemia (\%)} = 100 - \left(\frac{\text{\% of parasitemia of treated group}}{\text{mean \% parasitemia of control group}}\right) \times 100$$

2.5.2. Curative antiplasmodial activity (Rane's test)

The curative activity of MME was evaluated using the methods described earlier [15]. The inoculum was prepared by diluting 0.2 mL of Plasmodium berghei-infected donor blood with physiological saline to obtain approximately 1×10^7 parasitized erythrocytes per 0.2 mL. Each of the twenty-five mice was inoculated intraperitoneally with 0.2 mL of this suspension. The mice were randomly assigned to five groups as described above, and treatment with either MME doses, artemether/lumefantrine, or distilled water commenced 72 h post-infection and continued once daily for 3 consecutive days. The daily parasitemia levels were determined using blood smears and microscopic examination. Afterwards, the percentage of parasitemia was obtained using the following formula:

$$\text{Parasitemia (\%)} = \frac{\text{Number of parasitized RBCs} \times 100}{\text{Total RBC counted}}$$

The hemoglobin concentration was measured on days 0, 7, and 10 using Drabkin's method with slight modifications [16]. Also, the temperature of the animals was taken at days 0, 7, and 10.

2.6. Evaluation of the antipyretic activity

2.6.1. P. berghei-induced Pyrexia

The evaluation of *P. berghei*-induced antipyrexia was conducted alongside the curative antiplasmodial model, as described above. The temperature of the animals was taken on day 0 and then on days 7 and 10 after the administration of the different interventions to each group. Groups I–III received oral doses of MME at 100, 200, and 400 mg/kg, respectively; Group IV received artemether/lumefantrine (1:6 ratio, 4 mg/kg); and Group V received distilled water (10 mL/kg) as control.

2.6.2. Yeast-induced Pyrexia

The procedure described by Okokon *et al*. was adapted for this study [17]. The mice were randomly divided into five groups of five mice each. The basal temperature of the mice was measured (at 0 h) using a digital clinical thermometer. Subsequently, 20 % w/v aqueous suspension of yeast (10 mL/kg volume) was used to induce pyrexia in all mice. Temperature measurements were taken rectally at 1 h intervals for 4 h intervals, beginning 1 h post-yeast administration, and animals with a 1 °C were selected and grouped for the study. Groups I-III received oral treatments of MME (100, 200, and 400 mg/kg, respectively), whereas groups IV and V received oral treatments of paracetamol (10 mg/kg) and distilled water (10 mg/kg), respectively. The rectal temperatures of the groups were taken at 1h intervals for 4h.

2.7. Statistical analysis

Data were expressed as mean ± SEM. Statistical comparisons were performed using one-way ANOVA. Differences in mean values with $p < 0.05$ were considered statistically significant.

3. Results

3.1. Phytochemical analysis

The MME showed positive phytochemical reactions, indicating the presence of flavonoids, steroids, tannins, oils, proteins, alkaloids, saponins, terpenoids, reducing sugars, carbohydrates, and cardiac glycosides.

3.2. Oral acute toxicity of MME

There was no mortality in Phase 1, and the animals showed no signs of acute toxicity. In phase two, there was also no mortality even at the 5000 mg/kg dose.

3.3. Suppressive activity of MME on P. berghei-infected mice

The control group exhibited markedly elevated parasitemia levels, with a mean value of 25.20 ± 1.24%. In contrast, treatment with artemether/lumefantrine or the methanol extract of *Monodora myristica* (MME)

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Table 1. Suppressive activity of MME on *P. berghei*-infected mice.

Treatment	Dose (mg/kg)	Parasitemia (%)	Inhibition (%)/clearance
MME	100	4.20±.37**	83.33
MME	200	2.60±.40**	89.68
MME	400	1.40±.25***	94.44
Artem/Lum	4	1.20±.58***	95.24
D/W	10	25.20±1.24	0.00

Values are expressed as mean ± SEM; n=5; **p<0.01, ***p<0.001 significant difference relative to negative control; MME = methanol extract of *M. myristica* seed; Artem/Lum = Artemether/Lumefantrine; D/W = Distilled Water (mL/kg)

Table 2. Curative activity of MME on *P. berghei*-infected mice.

Treatment	Dose (mg/kg)	DAY 0	DAY 3	DAY 4	DAY 5
MME	100	26.60±1.54	21.20±1.16 (33.75)	10.00±0.45** (70.56)	4.60±0.51*** (87.50)
MME	200	27.40±1.33	18.00±1.41 (43.75)	8.80±0.67*** (74.12)	2.20±0.67*** (94.02)
MME	400	28.0±1.30	17.6±1.07 (45.00)	8.80±0.86*** (74.12)	1.80±0.58*** (95.11)
Artem/Lum	4	27.80±1.62	16.80±1.07 (47.5)	8.60±0.68*** (74.71)	2.00±0.32*** (94.57)
D/W	10	28.20±2.06	32.00±1.51	34.00±1.14	36.80±1.71

% Parasitemia ReductionValues are expressed as mean ± SEM; n=5; **p<0.01, ***p<0.001 significant difference relative to negative control; MME = methanol extract of *M. myristica* seed; Artem/Lum = Artemether/Lumefantrine; D/W = Distilled Water (mL/kg). Values in parentheses represent the percentage suppression of parasitaemia relative to the negative control group. For the control group, suppression is 0% by definition.

at all administered doses resulted in a statistically significant reduction in parasitemia ($p < 0.01$ and $p < 0.001$, respectively). The antiplasmodial activity of MME demonstrated a dose-dependent pattern, with the highest level of parasitemia inhibition (94.44%) observed at the dose of 400 mg/kg. Artemether/lumefantrine treatment achieved comparable inhibition of 95.24% (Table 1).

3.4. Curative activity of MME on P. berghei-infected mice

Administration of MME at doses of 100, 200, and 400 mg/kg elicited a statistically significant ($p < 0.01$; $p < 0.001$) and dose-dependent reduction in parasitaemia in *P. berghei*-infected mice. Notable parasitaemia clearance was evident from the third day of treatment with the extracts. The group treated with 400 mg/kg of MME exhibited the highest level of parasitaemia suppression (95.11%), which marginally exceeded that observed in the artemether/lumefantrine-treated group (94.57%) (Table 2).

3.5. Effect of MME on hemoglobin content

Haemoglobin concentrations exhibited a marked decline by day 3 post-infection across all experimental groups. However, progressive recovery was evident in all treatment groups on the days 7 and 10. By day 10, mice administered methanol extract of MME at doses of 100, 200, and 400 mg/kg demonstrated significantly elevated haemoglobin levels ($p < 0.001$) relative to the untreated control group. These haemoglobin values were comparable to those observed in the group treated with the standard antimalarial combination, artemether/lumefantrine (14.54 ± 0.04 g/dL) (Table 3).

3.6. Effect of MME on P. berghei-induced Pyrexia

Plasmodium berghei infection induced a febrile response characterized by a mean rectal temperature of 38.48 ± 0.18 °C in the untreated control group. Administration of the methanol extract of the plant (MME) at doses of 100, 200, and 400 mg/kg produced a statistically significant ($p < 0.05$), dose-dependent reduction in pyrexia on days 7 and 10 post-infection when compared with the untreated group. The highest dose (400 mg/kg) elicited the most pronounced antipyretic effect, which surpassed that observed with the standard artemether/lumefantrine treatment (Table 4).

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Table 3. Effect of methanol extract of MME on the hemoglobin content.

Treatment (mg/dl)	Dose (mg/kg)	Day 0 (mg/dl)	Day 3 (mg/dl)	Day 7 (mg/dl)	Day 10 (mg/dl)
MME	100	14.70±.24	14.14±.07	14.36±.06***	14.46±.05***
MME	200	14.66±.15	14.26±.05	14.30±.04***	14.42±.06***
MME	400	14.62±.17	14.18±.08	14.42±.07***	14.42±.09***
Artem/Lum	4	14.56±.14	14.12±.13	14.28±.11***	14.54±.04***
D/W	10	14.60±.17	14.04±.12	13.88±.10	13.76±.10

Values are expressed as mean ± SEM; n=5; ***p<0.001 significant difference relative to negative control; MME = methanol extract of *M. myristica* seed; Artem/Lum = Artemether/Lumefantrine; D/W = Distilled Water (mL/kg).

Table 4. Effect of MME on *P. berghei*-induced Pyrexia.

Treatment	Dose (mg/kg)	Day 0 (°C)	Day 7 (°C) (% °C reduction)	Day 10 (°C) (% °C reduction)
MME	100	38.68±0.28	37.04±0.14* (4.24)	37.14±0.53* (3.98)
MME	200	38.74±0.24	36.84±0.42* (4.90)	36.80±0.27* (5.01)
MME	400	38.88±0.22	36.60±0.40* (5.88)	36.84±0.46* (5.23)
Artem/Lum	5	38.20±0.22	36.58±0.31* (4.24)	36.72±0.38* (3.87)
D/W	10	38.48±0.18	38.52±0.38 (0.00)	38.26±0.46* (0.57)

Values are expressed as mean ± SEM; n=5; *p<0.05 significant difference relative to negative control; MME = methanol extract of *M. myristica* seed; Artem/Lum = Artemether/Lumefantrine; D/W = Distilled Water (mL/kg)

Table 5. Effect of MME on yeast-induced Pyrexia.

Treatment	Dose (mg/kg)	Baseline (°C)	After Induction (°C)	1 h (°C)	2h (°C)	3 h (°C)	4 h (°C)
MME	100	36.28±.44	38.28±.16	37.48±.20*** (2.09)	37.04±.186*** (3.24)	36.24±.264*** (5.33)	36.86±.211*** (3.71)
MME	200	36.24±.33	38.68±.16	37.54±.18*** (2.95)	36.90±.219*** (4.60)	36.34±.081*** (6.05)	36.34±.121*** (6.05)
MME	400	36.20±.36	38.04±.19	36.62±.30*** (3.73)	36.20±.197*** (4.84)	35.92±.231*** (5.57)	35.56±.186*** (6.52)
PCM	10	36.50±.35	38.44±.35	37.48±.37*** (2.49)	36.70±.371*** (4.53)	36.10±.230*** (6.09)	36.18±.183*** (5.88)
D/W	10	36.10±.39	39.06±.18	39.24±.216 (-0.46)	38.68±.261 (0.97)	38.52±.403 (1.38)	38.32±.124 (1.89)

Values are expressed as mean ± SEM; n=5; ***p<0.001 significant difference relative to negative control; MME = methanol extract of M. myristica seed; PCM = Paracetamol; D/W = Distilled Water (mL/kg). Values in parentheses indicate the percentage reduction in pyrexia (Δ°C %) compared to temperature after yeast induction.

3.7. Effect of MME on yeast-induced Pyrexia

The administration of Brewer's yeast induced a significant elevation in rectal temperature in all experimental groups. However, treatment with methanol extract of *M. myristica* (MME) at doses of 100, 200, and 400 mg/kg produced a statistically significant, dose-dependent reduction in rectal temperature ($p < 0.001$) relative to the negative control group. The most pronounced antipyretic effect was recorded at 4 h post-treatment in the group receiving 400 mg/kg of MME. In comparison, paracetamol exhibited a similar but comparatively lower antipyretic response (Table 5).

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4. Discussion

Despite decades of global intervention, malaria remains a resilient public health burden, disproportionately affecting populations in sub-Saharan Africa [18]. Although conventional antimalarial agents have significantly reduced malaria-related morbidity and mortality, their long-term efficacy is increasingly undermined by high recrudescence rates and the emergence of drug-resistant strains of Plasmodium. Consequently, there is a growing imperative to explore alternative therapeutic strategies, including the use of plant-derived natural products. Given that fever is a cardinal symptom of malaria, the present study investigated the antiplasmodial and antipyretic activities of the methanol extract of *Monodora myristica* (MME). Our findings demonstrate that MME possesses both antiplasmodial and antipyretic properties in experimental models.

In rodent models, *Plasmodium berghei* induces malaria through the rapid asexual proliferation of merozoites within red blood cells (RBCs). Within RBCs, the parasite progresses through the trophozoite and schizont stages, resulting in exponential merozoite multiplication [19]. Subsequent rupture of infected RBCs releases merozoites into the circulation, which precipitates clinical manifestations of malaria, such as fever, anaemia, and inflammation [20]. Malaria infection has also been shown to cause a reduction in the hemoglobin content. Through the rupture of RBCs caused by the multiplication of merozoites, there is a rapid loss of RBCs, and consequently, their hemoglobin content [21]. Also, haemoglobin reduction may occur through suppressed erythropoiesis, resulting in bone marrow dysfunction [22]. Antimalarial agents are generally classified as prophylactic (preventive), suppressive (early blood-stage or schizonticidal), or therapeutic (curative) agents or may possess more than one of these activities. Suppressive activity denotes the ability of a substance to suppress the multiplication of blood-stage parasites after infection has occurred, thereby limiting the progression of parasitaemia [23]. Curative activity, on the other hand, refers to the ability of a substance to clear off malaria parasite after an established malaria infection. This is essential because it assesses the ability of a substance to treat active malaria and its associated symptoms. Our findings demonstrated that MME exhibited a dose-dependent reduction in the level of the parasitemia, for the suppressive model. The 400 mg/kg MME group showed a comparable parasitemia inhibitory ability to the group administered the reference drug, artemether/lumefantrine. For the curative model, the 400 mg/kg MME group had a higher parasitemia reduction than the artemether/lumefantrine group, showing its potential as an effective antimalarial agent against established malaria infections. Additionally, MME significantly improved the hemoglobin content following treatment, showing comparable effects with the reference drug.

Malaria infection has been reported to impair erythropoiesis through bone-marrow dysfunction [24], resulting in anemia. The observed increase in hemoglobin levels suggests that MME may have mitigated malaria-induced suppression of erythropoiesis, leading to hemoglobin restoration. In this study, the antipyretic effect was evaluated using yeast and *P. berghei*. Upon yeast administration, a strong immune response occurs, leading to the production of inflammatory molecules such as interleukin-1, interleukin-6, and tumor necrosis factor [25]. These molecules stimulate the production of prostaglandin E2, which alters the activity of the hypothalamus. This, in turn, raises the set point temperature in the hypothalamus, leading to higher heat generation than heat loss [25]. Also, *P. berghei* causes pyrexia through similar mechanisms as the by-products of the parasite, acts as pathogen-associated molecular patterns which activate the immune cells and pro-inflammatory cytokines [26]. Our results showed a dose-dependent reduction in temperature across the MME doses. By day 7 and 10, the MME (400 mg/kg) elicited significant antipyretic reductions which were superior to those of artemether/lumefantrine. Other doses (100 and 200 mg/kg) also showed comparable temperature reductions with the reference drug. Similarly, all doses of MME showed a temperature reduction for the yeast-induced pyrexia in a dose-dependent manner. Notably, the 200 mg/kg and 400 mg/kg MME doses had a superior antipyretic effect than paracetamol (10 mg/kg) at 4 h. This shows the potential of *M. myristica* as a single agent with dual

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antipyretic and antiplasmodial activities, offering a promising alternative for the integrated management of malaria and its associated fever. Furthermore, with the relative safety profile of MME demonstrated in the acute toxicity tests, this extract can be applied in clinical settings as an alternative treatment option for malaria and fever, especially in low-resource settings. However, chronic toxicity tests are required to understand its long-term safety and potential delayed toxicities.

The observed pharmacological activities of MME may be attributed to the presence of bioactive phytochemicals, such as flavonoids, tannins, alkaloids, and saponins. Flavonoids, including quercetin and kaempferol, have been reported to exhibit both antiplasmodial and antipyretic effects. Ali and his colleagues conducted a study evaluating effects of quercetin in mouse models [27]. Their findings showed that in addition to the *P. berghei*-inhibitory effects of quercetin, it also led to the mitigation of cytokine storm during malaria infection. Similarly, studies have found the antimalarial effects of kaempferol and its ability to inhibit GSK3β—an important kinase found to have modulatory effects on inflammation, immune response and host response to malaria [28, 29]. Furthermore, ellagic and tannic acids from tannins found in many plants have been reported to possess antiplasmodial and antipyretic effects [30–32].

Since MME has shown antiplasmodial and antipyretic effects, further studies are essential to fully elucidate its mechanisms. Given the emergence of resistant strains for conventional antimalarial drugs, our study provides encouraging evidence for the further isolation and characterization of the active moiety responsible for the dual effects of *M. myristica,* as a potential alternative treatment option.

5. Conclusions

M. myristica showed effective antiplasmodial effect against *P. berghei* using the suppressive and curative models in infected mice. Also, it effectively reduced rectal temperatures in the *P. berghei*-induced and yeast-induced pyrexia. These findings justify the use of *M. myristica* in the treatment of malaria and fever in folkloric medicine.

Ethics approval

This study was conducted according to the ethical guidelines, and an ethical clearance certificate was obtained from the institutional review board of the Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka. Ethical Clearance Number: FPSRA/UNN/25/0151.

Authors' contributions

Conceptualization, C.E., C.S.N.; methodology, C.S.N.; formal analysis, C.E., C.E.A., O.P.E., C.S.N.; investigation, C.E., C.E.A., O.P.E., C.S.N.; writing – original draft preparation, C.E., C.E.A., O.P.E.; Writing – review and editing, C.E., C.E.A., O.P.E., C.S.N.; supervision, C.S.N.; project administration, C.E., C.E.A., O.P.E., C.S.N.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare that they have no conflict of interest.

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