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Original Article **Open Access**

Assessment of markers of platelet immune activation in malaria, tuberculosis and human immunodeficiency virus infection

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Abstract:

Background: Malaria, tuberculosis (TB) and human immunodeficiency virus (HIV) infection remain issues of public health concern in Nigeria. This study assessed parameters of platelet immune function with a view to understanding their role in the immune response against malaria, TB and HIV infection at the University of Calabar Teaching Hospital and Dr Lawrence Henshaw Memorial Hospital, Calabar, Nigeria.
Methodology: Following ethical approval and informed consent, 180 participants (males and females) aged 15-45 years were enrolled, comprising 90 malaria patients, 20 TB patients, 25 HIV patients, and 45 apparently healthy participants as control. Platelet indices were determined by haemocytometry. Platelet factor 4, P-selectin and cluster of differentiation 40 ligand (CD40L) were measured by enzyme linked immunosorbent assay (ELISA). One-way analysis of variance was used to analyse data, with statistical significance set at $p<0.05$.
Results: The platelet count of the TB patients was significantly higher ($p=0.017$) than that of malaria and HIV patients, and the control. The mean platelet volume was significantly increased ($p=0.001$) for HIV patients compared to malaria and TB patients, and the control. Similarly, platelet distribution width was significantly higher for HIV patients ($p=0.020$) compared to the other groups. Platelet factor 4 and CD40L levels were higher for HIV patients, followed by malaria and TB patients, compared to the control ($p=0.001$). P-selectin values were also significantly higher for malaria, TB and HIV patients compared to the control participants ($p=0.001$).
Conclusion: This study shows significant association of immune effectors such as platelet factor 4, CD40L and P-selectin released by platelets, with malaria, TB and HIV infections. Targeting these immune effectors may open new pathways for therapeutic interventions against these diseases.

Keywords: Platelets, immune activation, malaria, tuberculosis, human immunodeficiency virus.

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Évaluation des marqueurs de l'activation immunitaire plaquettaire dans le paludisme, la tuberculose et l'infection par le virus de l'immunodéficience humaine (VIH)

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Résumé:

Contexte: Le paludisme, la tuberculose (TB) et l'infection par le virus de l'immunodéficience humaine (VIH) demeurent des problèmes de santé publique préoccupants au Nigéria. Cette étude a évalué les paramètres de la fonction immunitaire plaquettaire afin de comprendre leur rôle dans la réponse immunitaire contre le paludisme, la tuberculose et l'infection par le VIH à l'hôpital universitaire de Calabar et à l'hôpital Dr Lawrence Henshaw Memorial, à Calabar, au Nigéria.
Méthodologie: Après approbation éthique et consentement éclairé, 180 participants (hommes et femmes) âgés de 15 à 45 ans ont été recrutés, comprenant 90 patients atteints de paludisme, 20 patients atteints de tuberculose, 25 patients atteints du VIH et 45 participants apparemment en bonne santé comme témoins. Les

indices plaquettaires ont été déterminés par hémocytométrie. Le facteur plaquettaire 4, la P-sélectine et le ligand du cluster de différenciation 40 (CD40L) ont été mesurés par dosage immuno-enzymatique (ELISA). Une analyse de variance à un facteur a été utilisée pour analyser les données, avec une signification statistique fixée à $p<0,05$.
Résultats: La numération plaquettaire des patients atteints de tuberculose était significativement plus élevée ($p=0,017$) que celle des patients atteints de paludisme et de VIH et du témoin. Le volume plaquettaire moyen était significativement augmenté ($p=0,001$) pour les patients atteints du VIH par rapport aux patients atteints de paludisme et de tuberculose et au témoin. De même, la largeur de distribution plaquettaire était significativement plus élevée pour les patients atteints du VIH ($p=0,020$) par rapport aux autres groupes. Les taux de facteur plaquettaire 4 et de CD40L étaient plus élevés chez les patients atteints du VIH, suivis des patients atteints de paludisme et de tuberculose, par rapport au groupe témoin ($p=0,001$). Les valeurs de P-sélectine étaient également significativement plus élevées chez les patients atteints de paludisme, de tuberculose et du VIH par rapport aux participants témoins ($p=0,001$).
Conclusion: Cette étude montre une association significative entre les effecteurs immunitaires, tels que le facteur plaquettaire 4, le CD40L et la P-sélectine libérés par les plaquettes, et les infections par le paludisme, la tuberculose et le VIH. Cibler ces effecteurs immunitaires pourrait ouvrir de nouvelles voies thérapeutiques contre ces maladies.

Mots-clés: Plaquettes, activation immunitaire, paludisme, tuberculose, virus de l'immunodéficience humaine.

Introduction:

Platelets (thrombocytes) are formed elements of blood alongside red and white blood cells. Their indispensable role in the haemostatic function of blood is well established; however, the role of platelets in immunity has been the subject of literature, opening up new insights into the contribution platelets make in immune response to infectious diseases and inflammatory states. Platelets are known to cover a broad range of functions. Besides their role in haemostasis, they have immunological functions and thus participate in the interaction between pathogens and host defense.

The role of platelets in immunity have been extended to include but not limited to intervention against infectious pathogens, recruitment of other immune cells, enhancement of effector cell functions, modulation of antigen presentation and amplification of the adaptive immune responses to infection (1). Platelets are able to sense invading pathogens and infection-induced inflammation; hence, they initiate an intense crosstalk with other arms of the innate and adaptive immunity, including neutrophils, monocytes/macrophages, dendritic cells, B cells and T cells. On stimulation by bacteria or thrombin, platelets release the content of their alpha-granules, which include bioactive peptides, such as chemokines and lymphokines (2).

Malaria, tuberculosis (TB) and human immunodeficiency virus (HIV) infection are major infectious diseases that have persisted as issues of public health concern globally and in Nigeria. One of the United Nations Sustainable Development Goals (SDGs) aims to "*Ensure healthy lives and promote well-being for all at all ages*". The World Health Organization (WHO) in line with the SDGs had set targets to reduce the burden and subsequently eradicate these infectious diseases between 2020 and 2030 (3,4,5). Assessing the immune function of platelets may improve our understanding of the immune response and the interaction between immunologic and inflammatory processes that greatly influences the pathogenesis of malaria, TB and HIV infection.

The objective of this study is to provide information on the immune function of platelets by determining parameters of platelet function and markers of inflammatory and immune response in the trio of malaria, TB and HIV infections. The findings of this study may reveal specific pathways and immunological markers that could be useful targets of preventive and therapeutic interventions. Overall, this could improve the care and management of malaria, TB and HIV patients and ultimately reduce the burden of these diseases in Nigeria.

Materials and method:

Study setting and ethical approval:

The study sites are University of Calabar Teaching Hospital and Dr Lawrence Henshaw Memorial Hospital, Calabar. These two centers are tertiary institutions designated for the treatment of HIV, Malaria and TB in Cross-River state, Nigeria. Ethical approval for this study was obtained from the Health Research Ethics Committee of University of Calabar Teaching Hospital (UCTH/HREC/33/Vol.III/036) and informed consent was obtained from all the participants.

Study design and participants enrolment:

Based on a case-control study design requiring no follow-up, a total of 180 study participants (males and females) within the age range of 15-45 years were enrolled. This comprised of 90 malaria, 20 TB and 25 HIV-infected participants including newly diagnosed patients and those on treatment, attending clinics in the two hospitals. Patients with co-morbidities and those who did not give consent were excluded from the study.

Forty-five apparently healthy participants were recruited as controls from among the staff and students of both hospitals. They were individuals who had been screened negative for latent TB infection (LTBI) using the

Mantoux test in the preceding six months. The control participants were also screened negative for malaria and HIV antibodies using RDT test and Determine HIV strip respectively. The diagnostic criteria for recruitment of control participants, malaria, TB and HIV patients are presented in Fig. 1.

Data and sample collection and laboratory analysis:

The socio-demographic data of all recruited participants were collected using a designed data collection form. Five milliliters (5ml) of venous blood were collected from each participant with minimum stasis; 2ml was added to ethylene diamine tetra-acetic acid (EDTA) to a final concentration of 2 mg/ml while 3ml was dispensed into a plain container. The samples were transported in cold chain to Haematology laboratory of the University of Calabar Teaching Hospital for analysis.

The sample in the plain container was allowed to clot and then centrifuged to obtain serum. The serum was dispensed into a separate container and stored at -20^{o}C until used for ELISA tests. Platelet counts, mean platelet volume, platelet distribution width and plateletcrit were determined for all participant samples by haemocytometry using an autoanalyzer. Platelet factor 4, P-selectin and CD40L were measured by ELISA technique for the 25 control participants, 20 malaria, 20 TB and 25 HIV patients.

Data analysis:

Results were expressed as mean±SD. One-way analysis of variance and post-hoc test on the Statistical Package for the Social Sciences (SPSS) version 22.0, was used to test hypotheses. P value < 0.05 was considered to be statistically significant.

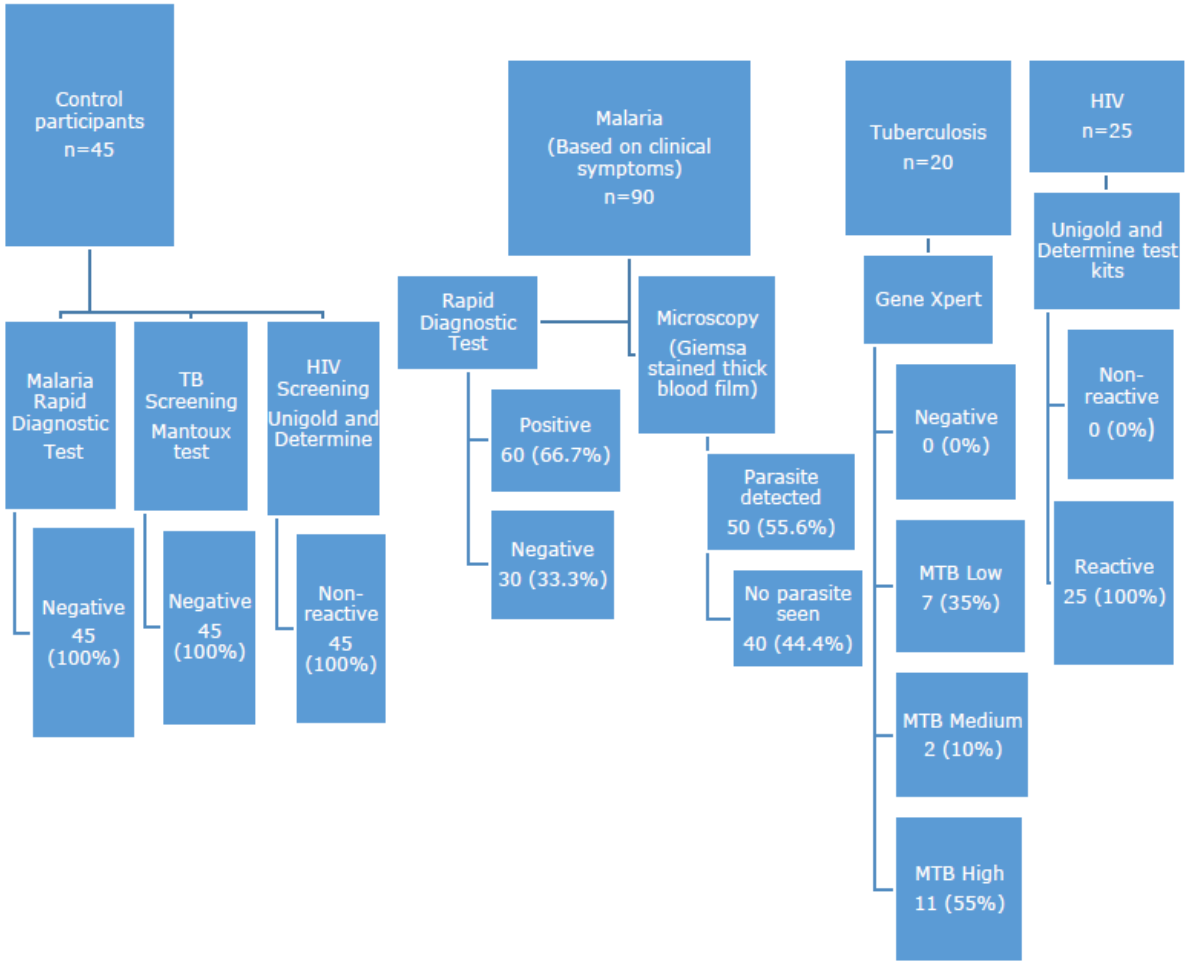

Fig 1: Diagnostic criteria for recruitment of malaria, tuberculosis and HIV patients, and the control participants

Results:

Table 1 shows the demographic data of the study participants. The control was equally distributed, 15 (33%) among three age groups of 15-24, 25-34 and 35-45 years; malaria patients were 15, 38 and 37 for the three age groups respectively. Tuberculosis patients were 4, 5 and 11 while HIV patients were 0, 3 and 22 for the three age groups respectively. The controls comprised 46.7% males and 53.3% females. The gender distribution for malaria was 25.6% males, 74.4% females, for TB 75% males, 25% females and for HIV 48% males and 52% females. Sixty percent of the control were single while 75.5% of malaria patients were married; TB patients were equally distributed (50.0%) each for single and married categories while the HIV patients comprised more of the married (60%).

Majority (75.5%) of the control as well as 50.0% of malaria patients and 40.0% of HIV patients had tertiary level of education while 55% of TB patients were secondary school leavers. The control were mostly students (55.6%), malaria and TB patients were spread across business operators (40% and 25%) and students (31.1% and 25%) while HIV patients comprised mostly of business operators (40%).

As shown in Table 2, the platelet count of TB patients was significantly higher (p= 0.017) when compared to the values for the control, malaria and HIV patients. The mean platelet volume significantly increased (p= 0.001) for HIV patients compared to malaria and TB patients, and the control. Similarly, platelet distribution width was significantly higher for HIV patients (p=0.020) compared to the other groups.

Table 3 shows that platelet factor 4, CD40L and P-selectin levels of malaria, TB and HIV patients were significantly higher (p= 0.001) in comparison with the control values. Post hoc analysis revealed that platelet factor 4 and CD40L were significantly higher for malaria compared to TB patients, as well as for HIV compared to TB patients. Also, platelet factor 4 was observed to be significantly higher for HIV compared to malaria patients.

Table 1: Socio-demographic characteristics of malaria, tuberculosis and HIV patients, and the control participants

Parameters	Control (%) (n=45)	Malaria patients (%) (n=90)	Tuberculosis patients (%) (n=20)	HIV patients (%) (n=25)
Age group (years)				
15-24	15 (33.3)	15 (16.7)	4 (20.0)	0
25-34	15 (33.3)	38 (42.2)	5 (25.0)	3 (12.0)
35-45	15 (33.3)	37 (41.1)	11 (55.0)	22 (88.0)
Gender				
Male	21 (46.7)	23 (25.6)	15 (75.0)	12 (48.0)
Female	24 (53.3)	67 (74.4)	5 (25.0)	13 (52.0)
Marital status				
Single	27 (60.0)	15 (16.7)	10 (50.0)	10 (40.0)
Married	18 (40.0)	68 (75.5)	10 (50.0)	15 (60.0)
Divorced	0	0	0	0
Widowed	0	7 (7.8)	0	0
Education				
Non-formal	0	8 (8.9)	2 (10.0)	0
Primary	3 (6.7)	14 (15.5)	3 (15.0)	8 (32.0)
Secondary	8 (17.8)	23 (25.6)	11 (55.0)	7 (28.0)
Tertiary	34 (75.5)	45 (50.0)	4 (20.0)	10 (40.0)
Occupation				
Civil/Public servants	20 (44.4)	10 (11.1)	3 (15.0)	8 (32.0)
Business/trading	0	36 (40.0)	5 (25.0)	10 (40.0)
Artisans	0	0	4 (20.0)	1 (4.0)
Students	25 (55.6)	28 (31.1)	5 (25.0)	4 (16.0)
Farmers	0	16 (17.8)	3 (15.0)	2 (8.0)

Table 2: Platelet count and indices of malaria, tuberculosis and HIV patients, and the control participants

Parameters	Control (n=45)	Malaria patients (n=90)	Tuberculosis patients (n=20)	HIV patients (n=25)	*p*-value
Platelet count x 10^9/L	179.80±58.37	225.47±98.09	276.63±61.45[a]	221.92±89.51	0.017
Mean platelet volume (fl)	9.18±0.57	8.87±0.57[c]	9.03±0.55	9.76±0.84[b]	0.001
Platelet distribution width	14.96±0.41	15.05±0.51	15.14±0.49	15.33±0.34[b]	0.020
Plateletcrit	0.95±0.43	0.20±0.10	0.27±0.12	0.23±0.10	0.664

Post Hoc: [a] = difference between control vs TB; [b] = difference between control vs HIV; [c] = difference between malaria vs HIV

Table 3: Platelet factor 4, CD40L and P-selectin levels of malaria, tuberculosis and HIV patients, and the control participants

Parameters	Control (n=25)	Malaria patients (n=20)	Tuberculosis patients (n=20)	HIV patients (n=25)	*p*-value
Platelet factor 4 (pg/ml)	21.83±0.95	53.61±2.85 [a]	40.92±4.34 [a, b]	67.08±3.76 [a, c, d]	0.001
CD40L (ng/ml)	3.33±1.21	6.79±1.00 [a]	5.11±1.29 [a, b]	6.80±1.13 [a, c]	0.001
P-selectin (pg/ml)	26.18±5.24	126.63±19.25 [a]	143.88±20.30 [a]	130.76±20.16 [a]	0.001

Post Hoc: [a]= Significantly different from control; [b]= difference between malaria and tuberculosis; [c]= difference between tuberculosis and HIV; [d]= difference between malaria and HIV; CD40L = Cluster of differentiation 40 ligand

Discussion:

Markers of platelet immune activation were assessed for malaria, TB and HIV patients in this study. About 33% of the malaria patients who were recruited based on clinical symptoms as determined by a physician were found to be negative for malaria using the rapid diagnostic test kit. Furthermore, the parasite was not detected microscopically for 44.4% of these malaria patients. A possible reason for this finding may be the practice of self-medication that is rampant in Nigeria (6,7). Several of these patients use over-the-counter antimalarial drugs and only present themselves at the clinic when symptoms do not improve. This underscores the need for proper laboratory testing especially in an endemic region where many patients are treated for malaria based on a combination of clinical symptoms that may or may not be caused by malaria parasite. The World Health Organization had directed that treatment for malaria should only be initiated after proper testing (8) but this is yet to be a reality in practice.

Most of the patients who presented with malaria, TB and HIV (83.3%, 80% and 100%) were between 25-45 years age group with lower percentage observed for patients <25 years of age. This reflects the enormous impact of these infectious diseases on the economically productive age group and is a cause for serious concern. Gender differences were observed among the patient population with more females presenting with malaria and more males presenting with TB. Females have been reported to contribute more to the burden of malaria with higher risk in child-bearing age as well as more frequent visits to health facilities as possible reasons (9). This is further confirmed as the findings of this study shows that more married persons were affected by malaria, with women being the majority.

One study suggested that women were more exposed to mosquito bites due to traditional roles which requires them to be outside during dangerous hours and the fact that self-medication was practiced more by men when compared to women (10). Again, it has been reported previously that TB affects more males than females due to socio-demographic factors and lifestyle that pre-disposes the male to infection with an airborne disease such as TB (11). Low socio-economic status has been implicated as a favorable factor for the acquisition of TB (12,13), and this is supported by the finding that 80% of the TB patients in this study had secondary school level of education and below.

Platelet count was observed to be significantly higher for TB patients in comparison to the control whereas the mean platelet volume which reflects the size and volume occupied by platelets, was found to be lower in malaria and higher in HIV infection with the platelet distribution width being higher in HIV infection. Increase in platelet count and mean platelet volume as observed is suggestive of platelet activation as a reaction to the presence of infection. Again, platelet factor 4, CD40L

and P-selectin levels were observed to be significantly higher in malaria compared to the apparently healthy controls in this study. Platelet activation and release of chemokines such as platelet factor 4 has been reported previously in malaria patients of Caucasian origin. The present study highlights the role platelets play in immunity against malaria in Africans, particularly for our local population in Nigeria.

Platelets contribute to the host defense against malaria through direct killing of the *Plasmodium* species (14-18). When platelets bind to malaria infected red cells, they become activated and release platelet factor 4 (CXCL4), a chemokine present in the alpha granules of platelets. Platelet factor 4 inhibits the growth of the malaria parasite resulting in parasite death; this is beneficial in malaria pathogenesis and may be useful in the formulation of antimalarial drugs targeted at enhancing the release and function of platelet factor 4. The CD40L is a transmembrane protein expressed on platelets, where it contributes to platelet activation and release of inflammatory mediators. Another transmembrane protein, P-selectin, is stored in the alpha granules of platelets and released upon platelet activation in inflammatory states (19). Increases in these proteins in malaria, TB and HIV infections as observed in this study, signifies platelet activation that suggests that platelets play a role in the immune response against these infections.

In our study, platelet factor 4, CD40L and P-selectin were observed to be significantly higher in TB patients, suggesting that platelet activation is part of the immune response against TB. This has been previously reported (20). Platelets engulf the bacteria and release antimicrobial peptides, which interact with internalized *M. tuberculosis*. In fact, *M. tuberculosis* modulates the production of cytokines by platelets. Furthermore, it has been shown that platelets are recruited into the granuloma formed in the late stages of TB. They internalize the *Mycobacterium* and produce host defense peptides (HDPs) such as RNase 7 and platelet factor 4 suggesting the participation of platelets in the immune response against TB through HDPs and production of cytokines (21).

The participation of platelets in infection and chronic inflammation such as TB is linked to their granules and organelles that contain chemokines, cytokines, enzymes and growth factors which function as immune effectors that are often released in response to damaged epithelium and interaction with leucocytes (22,23). Although these pro-inflammatory properties of platelets are beneficial, they could also lead to pathology in chronic infections such as TB. Hence, platelets appear to support the host response when the infection is extra-cellular, while in intracellular infections, they may contribute to immune evasion by TB pathogen, thereby making platelets a contributor to immunopathology (24). These two platelet effects may be explored as possible targets for anti-TB therapy.

Platelet factor 4, CD40L and P-selectin are released following activation of platelets and their levels were significantly increased in the HIV patients in our study. Platelets have been reported to harbor or hide HIV in infected person prior to the initiation of anti-retroviral therapy, thus infection of $CD4^+$ T cells via HIV-platelet complex is enhanced by platelet activation and subsequent platelet–T-cell complex formation (25,26). It has been suggested that platelets suppress HIV-1 spread in co-cultured T cells in a concentration-dependent manner and platelets containing granules inhibited HIV-1 spread in T cells more efficiently than degranulated platelets, indicating that granule content might exert antiviral activity. Indeed, supernatant from activated and degranulated platelets suppressed HIV-1 infection. The chemokine, CXCL4 (platelet factor 4) which is a major component of platelet granules, was found to block HIV-1 entry, and neutralization of CXCL4 in platelet supernatants largely abrogated their anti-HIV-1 activity. The inhibitory activity of platelet-derived CXCL4 suggests the role of platelets in the defense against infection by HIV-1 and potentially other pathogens (27). Patients with high levels of biomarkers of coagulation/inflammation such as CXCL4 are at an increased risk of developing non-AIDS defining serious illnesses such as cardiovascular diseases (28). This increased risk has serious implications for the HIV patients in our study.

The trio of malaria, TB and HIV infection induce a state of inflammation in the body. Infection-induced inflammation involves recruitment and activation of platelets, as observed in our study. Excessive activation of platelets may result in thrombosis, which could be localized or widespread, with possible consequences of organ dysfunctions (29,30). The most severe result of platelet activation as part of the immune response is the condition of disseminated intravascular coagulation, characterized by intense microvascular thrombosis and consumption of platelets (31,32). Thus, the participation of platelets in the immune response against malaria, TB and HIV, may be both beneficial and harmful.

Conclusion:

This study shows significant association of immune effectors such as platelet factor 4, CD40L and P-selectin released by platelets with malaria, TB and HIV infections. Targeting the functions of these immune effectors may open new pathways for therapeutic inter-

ventions against these diseases by the development of drugs that will enhance platelet immune response while addressing the detrimental effects of excessive platelet activation.

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Contributions of authors:

PA designed the study and wrote the first draft of the manuscript; EA performed the statistical analysis; JE managed the literature searches; All authors were involved in the laboratory analysis and the approval of the final manuscript.

Conflict of interest:

No conflict of interest is declared.

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