Tropical Journal of Pharmaceutical Research April 2025; 24 (4): 561-568
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
https://dx.doi.org/10.4314/tjpr.v24i4.12

Review Article

Modulating xanthine oxidase activity: A promising therapeutic strategy to reduce the severity and associated inflammatory reactions in malaria infection

Mukhtar Gambo Lawal[1,3], Abdullahi Sama'ila[2,3], Rusliza Basir[3]*

[1]Department of Microbiology, Faculty of Natural & Applied Sciences, [2]Department of Pharmacology, College of Health Sciences, Umaru Musa Yar'adua University, Katsina, Nigeria, [3]Department of Human Anatomy, Pharmacology Unit, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor Darul Ehsan, Malaysia

For correspondence: **Email: rusliza@upm.edu.my; **Tel:** +60-12-4747459; **ORCID:** https://orcid.org/0000-0003-3363-6630*

Sent for review: 8 January 2025 *Revised accepted: 21 April 2025*

Abstract

Malaria is a severe and often fatal disease that affects millions of people each year. More than fifty percent of human population worldwide is at risk of malaria. While antimalarial therapy is targeted at parasite elimination, the pathogenesis of malaria infection is particularly oxidative and inflammatory, involving the generation of reactive oxygen species (ROS). Xanthine oxidase (XO) is believed to be a potent source of ROS during malaria infection. ROS generated by this enzyme are a major contributor to oxidative stress and inflammation development. Consequently, free radical production and oxidative stress are responsible for the numerous complications in severe malaria. Therefore, effective treatment of the disease will require, in addition to the elimination of the parasite, a mechanism that reduces severe oxidative stress and inflammatory reactions associated with the disease. The pathophysiologic role of this enzyme is thus a potential target in malaria infection. Inhibition of XO activity is clinically effective in treating many inflammatory diseases, such as gout and prevention of cardiovascular disorders, therefore making this enzyme an attractive candidate for treating malaria inflammation. The present review focuses on the role of XO in malaria pathogenesis and the potential of enzyme inhibition as a therapeutic strategy to mitigate the severe inflammatory responses during malaria infection. Ultimately, the severity, complications and death associated with the disease are ameliorated by reducing the intensity of the inflammatory reactions during malaria infection.

Keywords: *Malaria, Oxidative stress, Inflammation, Xanthine oxidase, Inhibition*

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Malaria is an infectious disease caused by species of the genus *Plasmodium*. It is the most devastating parasitic disease that affects humans [1]. An increasing percentage of people worldwide are at risk of contracting malaria, making the disease a severe public health concern. The global malaria burden has continued to increase over the last 2 years. At present, there is an estimated disease burden of 263 million cases and an estimated malaria death toll of 597,000 in 83 malaria-endemic countries [2]. The WHO African region carries the highest malaria burden, with children under 5 accounting for about 76 % of deaths in the region [2].

The pathogenesis of malaria infection involves the build-up of free radicals, particularly reactive

oxygen and nitrogen species [3]. Generation of free radicals and subsequent development of oxidative stress have recently been shown to be responsible for the numerous complications in severe malaria [4]. Up-regulation of host oxidative enzymes, such as xanthine oxidase, during plasmodium infection generates ROS, which are major contributors in triggering oxidative stress and inflammation experienced during a malaria episode. In addition, XO in malaria has the ability to induce pro-inflammatory cytokines production in macrophages and dendritic cells [5].

Despite intensive attempts to control the disease, malaria continues to be a significant public health challenge throughout the world. The widespread antimalarial drug resistance [6] and associated side effects of existing antimalarials cause a major setback in attempts to eradicate the disease [7]. It is pertinent to note that resistance to the first-line treatment regimen has also become a serious problem for malaria control [8]. Currently, there is rising resistance to artemisinin-based combination therapy [9], and the problem has worsened due to the lack of effective, readily available vaccines [10] as well as ineffective vector management [9,11]. In addition, imported malaria is becoming a serious barrier to the efforts of some countries to eliminate the disease [12].

These prevailing challenges necessitate the quest for new, innovative and effective antimalarial treatment approaches, which may include new medications with different pharmacological targets. Xanthine oxidase has been implicated as one of the potent triggers of inflammation during malaria, with resultant progression to severe pathologies and complications. Accordingly, this study attempts to demonstrate that modulating the enzyme activity is a promising therapeutic strategy to reduce the severity and the associated inflammatory reactions during malaria infection. It could be a novel treatment approach for the management of malaria and eventually reduce the severity and mortality associated with the disease.

Collation of data on XO-induced oxidative stress in malaria

A search method that focused primarily on the most recent updates on malaria pathogenesis and identifying new drug targets was used to conduct this review. Data were collated by searching online literature databases such as Web of Science, NIH (National Library of Medicine), PubMed and Google Scholar. “Malaria case report updates”, “malaria pathogenesis”, “oxidative stress and inflammation in malaria”, “xanthine oxidase”, “inhibition of xanthine oxidase for disease management”, “adjuvants”, and a few more related search terms were the main research terms. To gather the most relevant and recent information, this review primarily included studies published from 2018 to date.

Oxidative stress and malaria

Malaria is a highly oxidative and inflammatory disease [5]. Oxidative stress has been shown to induce inflammation through ROS activation of NF-kB with subsequent release of inflammatory cytokines [13]. Previous studies have demonstrated that malaria infection induces inflammasome and caspase 1 activation [14] and this finding further revealed that ROS act as an effective signal for activation of inflammasomes in macrophages [5].

The pathophysiology of malaria infection is linked to oxidative stress, which generates ROS such as hydrogen peroxide (H_2O_2), superoxide anions (O_2^-), hydroxyl radicals (OH), and hydroxide ions (OH^-) [15,16]. During the blood phase of malaria infection, various sources contribute to oxidative stress. These include haem generated from direct infection of red blood cells by the *Plasmodium* parasite and degradation of haemoglobin. Additionally, the host’s immune response to infection plays a role, as it involves upregulation of oxidative enzymes and phagocytic oxidative burst. A study has shown that antimalarial drugs, including chloroquine, amodiaquine and artemisinin such as dihydroartemisinin and artesunate, also contribute to the oxidative stress in malaria as a result of their mode of action, which involves the generation of ROS and subsequently leads to the oxidative killing of the *plasmodium* parasites [5].

Numerous studies have explained how oxidative stress plays a part in the pathophysiology of malaria. Several researchers have reported elevated levels of oxidative stress in malaria patients with *P. falciparum* and *P. vivax* infections [17]. Higher levels of malondialdehyde (MDA), a very important biomarker of oxidative stress, were reported among paediatric patients with complicated malaria [18]. Similar observations of increased oxidative stress, as indicated by high MDA levels, were seen in patients with *Plasmodium falciparum* malaria infection [19,20]. Moreover, severe malaria was linked to increased oxidative stress among paediatric patients with *P. falciparum* infection [21].

Malaria infection is often associated with serious complications, especially when immediate diagnosis and effective therapy are not provided [22]. Reactive oxygen species produced during malaria infection elicit oxidative damage and inflict cellular damage on vital organs [22]. A more recent study also implicates oxidative stress as being responsible for the numerous complications in severe malaria [4]. A variety of manifestations, such as anaemia, thrombocytopenia, acute respiratory distress syndrome, pulmonary oedema, and hepatic and renal dysfunctions, are among the severe malaria complications [23]. Other severe manifestations include cerebral malaria [24], placental malaria, metabolic syndromes and hypoglycaemia [25]. It is pertinent to note that oxidative stress and the associated severe inflammatory responses accompanying malaria infection contribute to the significant morbidity and mortality associated with the disease. Blatt *et al* [26] reported oxidative stress as the cause of death in African children with severe malaria. A further study implicates oxidative stress-induced inflammation as the cause of multiple organ damage, leading to a high number of deaths in children and pregnant women worldwide [27].

Given the important involvement of oxidative stress in the pathogenesis of malaria and the implication of XO in the generation of ROS during malaria infection, this enzyme could be a key target for treating oxidative stress and inflammatory responses in malaria. Evidence from previous studies indicates that modulation of XO activity has proven to be clinically effective for the treatment of numerous inflammatory disorders, including gout [28,29], therefore making it an attractive candidate for tackling severe oxidative stress and inflammation in malaria infection.

Role of xanthine oxidase in the pathophysiology of malaria

The expression of XO and its activity have been shown to play paradoxical roles in many disease conditions. Free radicals generated from XO activity have a significant role in the innate immune system. It has been demonstrated that they have cytotoxic effects and induce apoptosis in some cancer cells [30]. On the other hand, XO-derived ROS contributes to cancer development [31]. Additionally, xanthine dehydrogenase gene expression was associated with decreased survival in lung adenocarcinoma patients [32].

Moreover, the enzyme activity has been associated with pro- and anti-inflammatory effects in many diseases. According to a recent study, excessive XO enzyme activity causes increased ROS levels, leading to oxidative damage [33] and subsequent development of oxidative stress as well as chronic inflammation [34]. Results from these studies suggest involvement of xanthine oxidase in several pathological conditions such as metabolic syndrome, endothelial dysfunctions and cardiovascular diseases [35-38]. Moreover, XO activity has been associated with the development of ischemia-reperfusion injury [39], haemolytic diseases and chronic inflammation [29]. In a more recent study, XO has been shown to exhibit pathological roles in cardiovascular diseases, heart failure, hypertension and atherosclerosis [33]. Findings by Ty *et al* [15] implicate XO as a host-derived source of inflammation in malaria. In another study, Iwalokun *et al* [16] reported elevated XO levels in paediatric patients with asymptomatic and symptomatic *P. falciparum* malaria. Moreover, a higher level of the enzyme was reported in *P. knowlesi* infection [40].

Reactive oxygen species (ROS) generated by xanthine oxidase have been shown to elicit a strong cytokine response in primary human monocyte-derived macrophages, resulting in the release of the inflammatory cytokine IL-1β as well as chemokines IL-8, CCL5 and CCL2 [15]. More evidently, higher levels of enzyme activity were seen to be correlated with inflammatory cytokines in malaria patients [15]. Furthermore, recent research has indicated that xanthine oxidase serves as a significant source of ROS, which leads to the activation of inflammasomes in macrophages (Figure 1) [41]. The enzyme also contributes to inflammation in malaria by promoting dendritic cell maturation and inducing cytokine release (Figure 1). In addition, xanthine oxidase-derived ROS causes parasite-triggered cytokine secretion and CD80 surface expression in dendritic cells [42].

During malaria infection, uric acid is produced due to the action of XO on hypoxanthine. Although uric acid plays an important physiological role, contributing to more than half of the blood plasma's antioxidant capability in humans [43], it also exhibits a pathological role. Evidence indicates that uric acid activates immune cells and stimulates the production of inflammatory cytokines during malaria infection [44]. This dual role underscores the complex involvement of uric acid in both physiological defence mechanisms and pathological processes associated with malaria [44]. Uric acid from

Plasmodium-infected erythrocytes stimulates the secretion of tumour necrosis factor in dendritic cells [45]. Additionally, uric acid levels have been shown to increase in malaria patients with greater disease severity [44], suggesting that its elevated levels may contribute to the disease's pathophysiology [43].

Potential role of XO inhibition as a drug target for malaria

Inhibition of xanthine oxidase activity is targeted at reducing ROS and uric acid generation, thereby preventing the development of oxidative stress and the associated oxidative damage. Remarkably, several pharmacological XO inhibitors have been widely described; among these is allopurinol [46], a drug that has been in use for a long time. Other potent XO inhibitors include febuxostat and topiroxostat [47,48]. Furthermore, potent inhibitory activity against XO has been exhibited by natural compounds, including extracts from plants [49]. Higher inhibition of XO was displayed by the flavonoids kaempferol, quercetin and isorhamnetin compared to the conventional drug allopurinol [50]. Suppression of XO activity has been a successful treatment approach for several diseases [51]. The enzyme has been a crucial target for the therapy of hyperuricaemia and gout [46]. In addition, the development of XO inhibitors has resulted in important advances in the treatment of oxidative damage, neurological disorders and neuropsychiatric conditions as well as in the management of reperfusion injury [52].

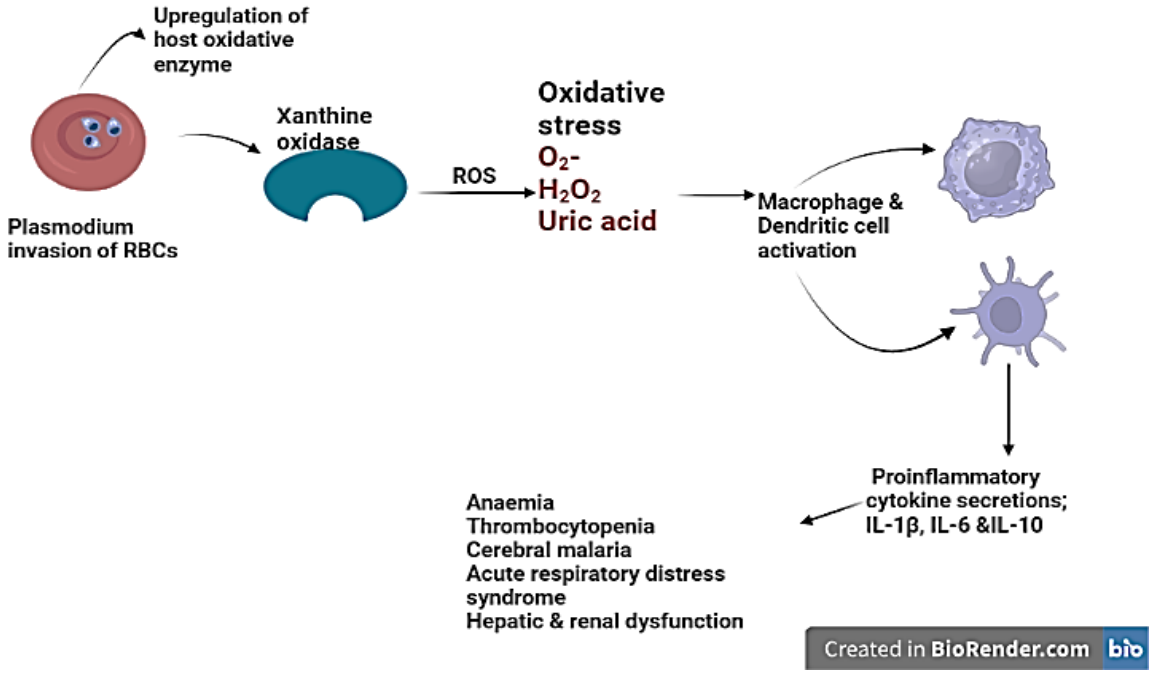

Figure 1: Pathogenic involvement of Xanthine oxidase in oxidative stress and malaria

Table 1: Studies demonstrating xanthine oxidase inhibition in malaria

Type of extract	Plant	Effect on XO	Reference
Methanol extract	*Achillea filipendulina*	Significant XO inhibitory activity IC_{50} value=12.87 µg/mL	[53]
Methanol extract	*Alcea glabrata*	Significant XO inhibitory activity IC_{50}value=0.37±0.12 mg/mL	[54]
2-aminoanthraquinone	Synthetic	57.45% inhibitory effect IC_{50} value=81.57 µM	[55]
Acacetin	*Potentilla evestita*	11.92±0.01 µM	[56]
Chrysin		73.74±0.02 µM	
Umbelliferon		97.12±0.01 µM	

Inhibition of XO may provide a potential therapeutic intervention for malaria, similar to its success in treating other inflammatory disease conditions. Since malaria has been well recognized as an oxidative and inflammatory disease, therefore, effective treatment of the disease will require, in addition to the elimination of the parasite, a mechanism that reduces severe oxidative stress and inflammatory reactions associated with the disease. As seen in the treatment of other disease conditions in which XO inhibition has been successful, inhibition of the enzyme activity may offer a potential therapeutic intervention for malaria. Therapy that restores and sustains oxidative equilibrium in patients with malaria may help avert the fatal consequences associated with the disease [5]. Findings from previous studies suggest that inhibiting ROS generation could represent a potential adjuvant therapeutic strategy and that targeting XO may be beneficial for adjunctive therapy in malaria [3]. It is important to note that, while a few studies have explored inhibition of xanthine oxidase (XO) activity for addressing severe oxidative-related inflammatory responses in malaria, most have only demonstrated enzyme suppression *in vitro*, as shown in Table 1. Further research, including both *in vivo* and *in silico* studies identifying effective targeted inhibitors against XO activity in malaria, is recommended.

CONCLUSION

The fight against malaria is crucial for global public health; however, it has always posed challenges. Therefore, the search for novel therapeutic approaches is necessary, potentially identifying new drug targets. The enzyme, xanthine oxidase, appears to be a promising therapeutic target in malaria since the severity and complications associated with the disease are driven by xanthine oxidase-produced ROS that cause oxidative stress and consequently lead to excessive inflammatory reactions. Thus, modulating its activity is a promising therapeutic strategy for alleviating the severity of inflammatory responses associated with the disease, minimizing the adverse effects and improving patient outcomes. Further research is necessary to confirm the effectiveness of XO inhibition in the management of malaria, and in essence, to identify and develop effective targeted inhibitors against XO activity.

DECLARATIONS

Acknowledgement

None.

Ethical approval

None provided.

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

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

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Mukhtar Gambo Lawal - conceptualized the study, performed literature search and drafted the manuscript; Abdullahi Samaila - Reviewed and edited the manuscript; Rusliza Basir - Made critical revision and contributed to the final version of the manuscript. All authors read and approved the final copy of the manuscript for publication.

REFERENCES

1. *Lee WC, Mahmud R, Perumal S, Ismail S, Basir R. In vivo antimalarial potential of Tinospora crispa Miers in mice and identification of the bioactive compound. Pharmacogn Mag 2020; 16(67): 76-82.*
2. *WHO World Malaria Report, 2024. https://www.who.int/news-room/fact-sheets/detail/malaria#:~:text=Disease%20burden,Republic%20of%20Tanzania%20(4.3%25). 11 Dec, 2024*
3. *Varela ELP, Gomes ARQ, da Silva Barbosa Dos Santos A, de Carvalho EP, Vale VV, Percário S. Potential benefits of lycopene consumption: rationale for using it as an adjuvant treatment for malaria patients and in several diseases. Nutrients 2022; 14(24): 5303. doi: 10.3390/nu14245303. PMID: 36558462; PMCID: PMC9787606.*
4. *Buthelezi MN, Masia KJ, Masamba P, Simelane MBC, Kappo AP. Understanding the interplay of malarial pathogenesis, host immune response and oxidative stress: Implications for disease progression and*

therapeutic strategies, Aspects of Molecular Medicine, 2025; 5: 100082, ISSN 2949-6888, https://doi.org/10.1016/j.amolm.2025.100082.

5. *Vasquez M, Zuniga M, Rodriguez A. Oxidative stress and pathogenesis in malaria. Front Cell Infec Microbiol 2021; 11: 768182. https://doi.org/10.3389/fcimb.2021.768182*
6. *Basir R, Chan KL, Yam MF, Othman F, Abdullah WO, Aris M, Moklas M, Saad A, Rahim A, Ismail IS. Antimalarial activity of selected Malaysian medicinal plants. Phytopharmacol 2012; 3(1): 82-92*
7. *Enechi OC, Amah CC, Okagu IU, Ononiwu PC, Nweke AC, Ugwuanyi TC, Ajibo EA, Nweze AC, Chukwurah BC. Sida acuta Burm. f. leaves ethanol extract ameliorates haematological and biochemical alterations induced by Plasmodium berghei ANKA-65 in mice. Clinical Phytosci 2021; 7(78): 1-12. https://doi.org/10.1186/s40816-021-00317-w*
8. *Alkandahri MY, Berbudi A, Subarnas A. Evaluation of experimental cerebral malaria of curcumin and kaempferol in Plasmodium berghei ANKA-infected mice. Pharmacogn J 2022; 14(6): 905-911.*
9. *Oladipo HJ, Tajudeen YA, Oladunjoye IO, Yusuff SI, Yusuf RO, Oluwaseyi EM, AbdulBasit MO, Adebisi YA, El-Sherbini MS. Increasing challenges of malaria control in sub-Saharan Africa: Priorities for public health research and policymakers. Ann Med Surg (Lond) 2022; 81: 104366. doi: 10.1016/j.amsu.2022.104366. PMID: 36046715; PMCID: PMC9421173.*
10. *Mubaraki MA, Hafiz TA, Al-Quraishy S, Dkhil MA. Oxidative stress and gene regulation of cerebral malaria upon Zizyphus spina-christi treatment in a murine model. Microb Pathog 2017; 107: 69-74. doi: 10.1016/j.micpath.2017.03.017. Epub 2017 Mar 21. PMID: 28336326.*
11. *Perera R, Wickremasinghe R, Newby G, Caldera A, Fernando D, Mendis K. Malaria control, elimination, and prevention as components of health security: a review. Am J Trop Med Hyg 2022; 107(4): 747-753. doi: 10.4269/ajtmh.22-0038. PMID: 36067989; PMCID: PMC9651538.*
12. *Shahandeh K, Basseri HR. Challenges and the Path Forward on malaria elimination intervention: a systematic review. Iran J Public Health 2019; 48(6): 1004-1013. PMID: 31341841; PMCID: PMC6635336.*
13. *Lingappan K. NF-κB in oxidative stress. Curr Opin Toxicol 2018; 7: 81-86. doi: 10.1016/j.cotox.2017.11.002. Epub 2017 Nov 7. PMID: 29862377; PMCID: PMC5978768.*
14. *Ataide MA, Andrade WA, Zamboni DS, Wang D, Souza Mdo C, Franklin BS, Elian S, Martins FS, Pereira D, Reed G, et al. Malaria-induced NLRP12/NLRP3-dependent caspase-1 activation mediates inflammation and hypersensitivity to bacterial superinfection. PLoS Pathog 2014; 10(1): e1003885. doi: 10.1371/journal.ppat.1003885. Epub 2014 Jan 16. Erratum in: PLoS Pathog 2014; 10(6):e1004258. PMID: 24453977; PMCID: PMC3894209.*
15. *Ty MC, Zuniga M, Götz A, Kayal S, Sahu PK, Mohanty A, Mohanty S, Wassmer SC, Rodriguez A. Malaria inflammation by xanthine oxidase-produced reactive oxygen species. EMBO Mol Med 2019; 11(8): e9903. doi: 10.15252/emmm.201809903. Epub 2019 Jul 2. PMID: 31265218; PMCID: PMC6685105.*
16. *Iwalokun BA, Bamiro SB, Ogunledun A. Levels and interactions of plasma xanthine oxidase, catalase and liver function parameters in Nigerian children with Plasmodium falciparum infection. APMIS 2006; 114(12): 842-850. Doi: 10.1111/j.1600-0463.2006.apm_457.x. PMID: 17207084.*
17. *Pabón A, Carmona J, Burgos LC, Blair S. Oxidative stress in patients with non-complicated malaria. Clin Biochem 2003; 36(1): 71-78. doi: 10.1016/s0009-9120(02)00423-x. PMID: 12554064.*
18. *Nsiah K, Bahaah B, Oppong Afranie B, Koffie S, Akowuah E, Donkor S. Oxidative stress and hemoglobin level of complicated and uncomplicated malaria cases among children: a cross-sectional study in Kumasi metropolis, Ghana. J Trop Med 2019; 2019: 8479076. Doi: 10.1155/2019/8479076. PMID: 31360173; PMCID: PMC6642756.*
19. *Atiku SM, Louise N, Kasozi DM. Severe oxidative stress in sickle cell disease patients with uncomplicated Plasmodium falciparum malaria in Kampala, Uganda. BMC Infect Dis 2019; 19(1): 600. doi: 10.1186/s12879-019-4221-y. PMID: 31288760; PMCID: PMC6617886.*
20. *Babalola AS, Jonathan J, Michael BE. Oxidative stress and anti-oxidants in asymptomatic malaria-positive patients: A hospital-based cross-sectional Nigerian study. Egypt J Intern Med 2020; 32(1): 1-8. https://doi.org/10.1186/s43162-020-00024-x*
21. *Abdullahi IN, Musa S, Emeribe AU, Muhammed M, Mustapha JO, Shuwa HA, Haruna S, Abubakar SD, Billyrose OMA, Bakare M. Immunological and anti-oxidant profiles of malarial children in Abuja, Nigeria. Biomedicine (Taipei) 2021; 11(1): 41-50. doi: 10.37796/2211-8039.1010. PMID: 35223394; PMCID: PMC8823466.*
22. *Mazen MJA, Andrew WTR. Regulation of expression of reactive oxygen intermediates during Plasmodium infection to reduce immunopathology provides a possible antioxidant adjuvant to enhance anti-malarial drug therapy. Intern J Clin Microbiol 2017; 1(1): 8-16. https//doi.org/10.14302/issn.2690-4721.ijcm-17-1676*
23. *Ohiagu FO, Chikezie PC, Ahaneku CC, Chikezie CM, Law-Obi FC. Pathophysiology of severe malaria infection. Asian J Health Sci 2021; 7(2): ID22.*
24. *Wassmer SC, Taylor TE, Rathod PK, Mishra SK, Mohanty S, Arevalo-Herrera M, Duraisingh MT, Smith JD. Investigating the pathogenesis of severe malaria: a multidisciplinary and cross-geographical approach. Am J Trop Med Hyg 2015; 93(3 Suppl): 42-56. doi: 10.4269/ajtmh.14-0841. Epub 2015 Aug 10. PMID: 26259939; PMCID: PMC4574273.*
25. *Ioannidis LJ, Nie CQ, Hansen DS. The role of chemokines in severe malaria: more than meets the*

eye. Parasitol 2014; 141(5): 602-613. Doi: 10.1017/S0031182013001984. Epub 2013 Dec 13. PMID: 24476686; PMCID: PMC3962270.

26. *Blatt DB, Hanisch B, Co K, Datta D, Bond C, Opoka RO, Cusick SE, Michelow IC, John CC. Impact of oxidative stress on risk of death and readmission in African children with severe malaria: A prospective observational study. J Infect Dis 2022; 226(4): 714-722. doi: 10.1093/infdis/jiac234. PMID: 35678643; PMCID: PMC9890907.*
27. *Bhatt D, Kumar S, Kumar P, Bisht S, Kumar A, Maurya AK, Pal A, Bawankule DU. Rutin ameliorates malaria pathogenesis by modulating inflammatory mechanisms: an in vitro and in vivo study. Inflammopharmacol 2022; 30(1): 159-171. doi: 10.1007/s10787-021-00920-w. Epub 2022 Jan 21. PMID: 35064431.*
28. *Rahman S, Hridy UK, Alam M, Begum R, Hossain MA, Sarkar KK, Saha K, Barman AK, Biswas NN. Antioxidant, xanthine oxidase (XO) inhibitory, hypouricemic effect evaluation and GCMS analysis of ethanolic extract of Piper chaba stem: Supported by in vitro, in vivo, and molecular docking experiments. Phytomed Plus 2024; 4(4): 100652, ISSN 2667-0313, https://doi.org/10.1016/j.phyplu.2024.100652*
29. *Huang CY, Chang YY, Chang ST, Chang HT. Xanthine oxidase inhibitory activity and chemical composition of Pistacia chinensis leaf essential oil. Pharmaceutics 2022; 14(10): 1982. doi: 10.3390/pharmaceutics14101982. PMID: 36297418; PMCID: PMC9609098.*
30. *Xu H, Li C, Mozziconacci O, Zhu R, Xu Y, Tang Y, Chen R, Huang Y, Holzbeierlein JM, Schöneich C, Huang J, Li B. Xanthine oxidase-mediated oxidative stress promotes cancer cell-specific apoptosis. Free Radic Biol Med 2019; 1: 139: 70-79. doi: 10.1016/j.freeradbiomed.2019.05.019.*
31. *Chen Mm, Meng Lh. The double-faced role of xanthine oxidoreductase in cancer. Acta Pharmacol Sin 2022; 43: 1623–1632. https://doi.org/10.1038/s41401-021-00800-7*
32. *Tavassoly I, Hu Y, Zhao S, Mariottini C, Boran A, Chen Y, Li L, Tolentino RE, Jayaraman G, Goldfarb J, et al. Genomic signatures defining responsiveness to allopurinol and combination therapy for lung cancer identified by systems therapeutics analyses. Mol Oncol 2019; 13(8): 1725-1743. doi: 10.1002/1878-0261.12521. Epub 2019 Jul 10. PMID: 31116490; PMCID: PMC6670022.*
33. *Rullo R, Cerchia C, Nasso R, Romanelli V, Vendittis ED, Masullo M, Lavecchia A. Novel reversible inhibitors of xanthine oxidase targeting the active site of the enzyme. Antioxidants 2023; 12(4): 825. Available from: http://dx.doi.org/10.3390/antiox12040825*
34. *Kotozaki Y, Satoh M, Nasu T, Tanno K, Tanaka F, Sasaki M. Human plasma xanthine oxidoreductase activity in cardiovascular disease: evidence from a population-based study. Biomed 2023; 11(3): 754. doi: 10.3390/biomedicines11030754. PMID: 36979733; PMCID: PMC10045414.*
35. *Battelli MG, Bortolotti M, Polito L, Bolognesi A. The role of xanthine oxidoreductase and uric acid in metabolic syndrome. Biochim Biophys Acta Mol Basis Dis 2018; 1864(8): 2557-2565. doi: 10.1016/j.bbadis.2018.05.003. Epub 2018 May 5. PMID: 29733945.*
36. *Förstermann U. Uncoupling of endothelial nitric oxide synthase in cardiovascular disease and its pharmacological reversal. Nitric Oxide (Second Edition) 2010; 139-167. https://doi.org/10.1016/B978-0-12-373866-0.00005-8*
37. *Laurindo, FR. Redox cellular signaling pathways in endothelial dysfunction and vascular disease. Endothel Cardiovasc Dis 2018; 127-145. https://doi.org/10.1016/B978-0-12-812348-5.00010-6*
38. *Polito L, Bortolotti M, Battelli MG, Bolognesi A. Xanthine oxidoreductase: A leading actor in cardiovascular disease drama. Redox Biol 2021; 48: 102195. doi: 10.1016/j.redox.2021.102195. Epub ahead of print. PMID: 34844041; PMCID: PMC8636850.*
39. *Fujioka H, Koike T, Imamura T, Kakeshita K, Yamazaki H, Kinugawa K. Implication of changes in xanthine oxidase activity following hemodialysis. BMC Nephrol 2023; 24(1): 13. https://doi.org/10.1186/s12882-023-03062-z*
40. *Srivastava P, Puri SK, Dutta GP, Pandey VC. Status of oxidative stress and antioxidant defences during Plasmodium knowlesi infection and chloroquine treatment in Macaca mulatta. Int J Parasitol 1992; 22(2): 243-245. doi: 10.1016/0020-7519(92)90109-x. PMID: 1316884.*
41. *Canton M, Sánchez-Rodríguez R, Spera I, Venegas FC, Favia M, Viola A, Castegna A. Reactive oxygen species in macrophages: sources and targets. Front Immunol 2021; 12: 734229. doi: 10.3389/fimmu.2021.734229. PMID: 34659222; PMCID: PMC8515906.*
42. *Götz A, Ty MC, Rodriguez A. Oxidative stress enhances dendritic cell responses to Plasmodium falciparum. Immunohorizons 2019; 3(11): 511-518. doi: 10.4049/immunohorizons.1900076. PMID: 31690559.*
43. *El Ridi R, Tallima H. Physiological functions and pathogenic potential of uric acid: a review. J Adv Res 2017; 8(5): 487-493. doi: 10.1016/j.jare.2017.03.003. Epub 2017 Mar 14. PMID: 28748115; PMCID: PMC5512149.*
44. *Lopera-MesaTM, Mita-Mendoza NK, Doumbia S, Konaté D, Doumbouya M, Gu W, TraoréKS, Diakité S A, Remaley AT, Anderson JM, et al. Plasma uric acid levels correlate with inflammation and disease severity in Malian children with Plasmodium falciparum malaria. PLoS ONE 2012; 7(10), e46424. https://doi.org/10.1371/journal.pone.0046424*
45. *Orengo JM, Evans JE, Bettiol E, Leliwa-Sytek A, Day K, Rodriguez A. Plasmodium-induced inflammation by uric acid. PLoS Pathog 2008; 4(3): e1000013. doi: 10.1371/journal.ppat.1000013. PMID: 18369465; PMCID: PMC2267007.*

46. Pacher P, Nivorozhkin A, Szabó C. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. Pharmacol Rev 2006; 58(1): 87-114. doi: 10.1124/pr.58.1.6. PMID: 16507884; PMCID: PMC2233605.
47. Bredemeier M, Lopes LM, Eisenreich MA, Hickmann S, Bongiorno GK, d'Avila R, Morsch ALB, da Silva Stein F, Campos GGD. Xanthine oxidase inhibitors for prevention of cardiovascular events: A systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 2018; 18(1): 24. doi: 10.1186/s12872-018-0757-9. PMID: 29415653; PMCID: PMC5804046.
48. Cicero FG, Fogacci F, Cincione RI, Tocci G, Borghi C. Clinical effects of Xanthine oxidase inhibitors in hyperuricemic patients. Med Princ Pract 2021; 30(2): 122-130. https://doi.org/10.1159/000512178
49. Zhou S, Huang G. The inhibitory activity of natural products to xanthine oxidase. Chem Biodivers 2023; 20(5): e202300005. doi: 10.1002/cbdv.202300005. Epub 2023 May 2. PMID: 37070234.
50. Ajala OS, Ayeleso AO, Owolabi M, Akinleye MO, Ukpo G. Xanthine oxidase inhibitory potentials of flavonoid aglycones of Tribulus terrestris: in vivo, in silico and in vitro studies. Fut Pharm Sci 2022; 8: 58
51. Duong NT, Vinh PD, Thuong PT, Hoai NT, Thanh LN, Bach TT, Nam NH, Anh NH. Xanthine oxidase inhibitors from Archidendron clypearia (Jack.) I.C. Nielsen: Results from systematic screening of Vietnamese medicinal plants. Asian Pac J Trop Med 2017; 10(6): 549-556. doi: 10.1016/j.apjtm.2017.06.002. Epub 2017 Jun 15. PMID: 28756918.
52. Malik N, Dhiman P, Sobarzo-Sanchez E, Khatkar A. Flavonoids and anthranquinones as xanthine oxidase and monoamine oxidase inhibitors: a new approach towards inflammation and oxidative stress. Curr Top Med Chem 2018; 18(25): 2154-2164. doi: 10.2174/1568026619666181120143050. PMID: 30465507.
53. Asnaashari S, Marefat S, Vatankhah AM, Moghaddam SB, Delazar A, Hamedeyazdan, S. Bioactivity assays and phytochemical analysis upon Achillea filipendulina, focusing on xanthine oxidase inhibitory and antimalarial properties. BJBAS 2023; 12(1): 1-12. https://doi.org/10.1186/s43088-023-00385-6
54. Pirmohammadi Y, Asnaashari S, Nazemiyeh H, Hamedeyazdan S. Bioactivity assays and phytochemical analysis upon Alcea glabrata; focusing on xanthine oxidase inhibitory and antimalarial properties. Toxicon 2023; 229: 107140. doi: 10.1016/j.toxicon.2023.107140. Epub 2023 Apr 28. PMID: 37119859.
55. Rauf A, Khan R, Khan H, Jehan N, Akram M, Ahmad Z, Muhammad N, Farooq U, Khan A. In vitro antimalarial and xanthine oxidase inhibition of 2-Aminoanthraquinone. Pak J Pharm Sci 2016; 29(2): 429-432. PMID: 27087090.
56. Rauf A, Khan R, Khan H, Khan I, Akram M. Xanthine oxidase inhibition of bioactive constituents isolated from Potentilla evestita. J Chem Soc Pak 2016; 38(1).