The Link between Malaria and Ferroptosis - A Review

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Abstract:
Ferroptosis is an iron-dependent cell death characterized by extensive lipids peroxidation, dysfunctional glutathione-dependent antioxidant enzyme system, and alterations in the morphology of the mitochondrial membrane. This cell death plays a role in the pathogenesis of diabetes, neurological disorders, cardiovascular diseases, arthritis, and cancer. Accumulating evidence suggests that ferroptosis is involved in the pathogenesis of malaria. This evidence includes plasmodium-induced biochemical changes that could affect the susceptibility of host red blood cells and the parasite to ferroptosis and the role of ferroptosis in reducing parasite survival at the liver stage. Ferroptosis is induced by iron-dependent oxidative stress. Given that oxidative stress is involved in the pathogenesis of malaria, ferroptosis could also be involved. Furthermore, the frontline anti-malarial compound dihydroartemisinin exerts an anti-cancer effect through a ferroptosis-mediated mechanism. This suggests that ferroptosis induction could be one of its mechanisms of action against Plasmodium. In this review, we discussed the link between malaria and ferroptosis. Studying ferroptosis could reveal novel biochemical mechanisms underlying the pathogenesis of malaria. It may also unravel new modes of action of anti-malarial drugs, the biochemical basis for low drug efficacy, and promising molecular targets for the development of new anti-plasmodial compounds.

Keywords: **Anti-oxidants and Free radicals, Ferroptosis, Malaria, *Plasmodium*.**

1.0 Introduction

1.1 Malaria

The term malaria has its root in the Mediaeval Italian word: "*mala aria*" meaning "bad air". The disease was so named due to its association with the foul odour of swamps and marshland areas [1]. Charles Louis Alphonse Laveran (1845-1922) discovered the causative parasite *Plasmodium* in the blood of a malaria patient [2]. Subsequent work affirmed that malaria is an infectious blood-borne disease caused by the protozoan *Plasmodium*, which is carried and transmitted by female *anopheles* mosquitoes breeding in swampy and marshland areas contrary to the Italian "bad air" myth which suggests that malaria came from the bad air of swamps.

Malaria remains a major parasitic infectious disease, especially in sub-Saharan Africa [3]. This tropical disease characterised by acute blood loss resulting in severe anaemia and death is transmitted by the female *Anopheles* mosquito during blood meals on humans mostly from dusk to dawn in endemic areas [4]. Four species of the *Plasmodium* parasite: Plasmodium *falciparum*, *P. vivax*, *P. ovale* (with two subspecies *P. ovale wallickeri and P. ovale curtisi*), and *P. malariae* were identified as causative agents of the disease in humans [5, 6]. Recently identified specie, *P. knowlesi* which primarily infect *Macaca fascicularis* monkeys was also shown to result in the disease in humans [7]. Other *Plasmodium* species notably *P. chabaudi*, *P. yoelii*, *P. vinckei*, and *P. berghei* are known to infect rodents with similar disease presentation as that of human infection and hence are used as models for *in vivo* study of parasite biology, disease pathology, and antimalarial drug screening [8]. In addition to the simian parasite *P. knowlesi*, other species including *P. brasilianum* and *P. cynomolgi* that primarily infect non-human primates have been shown to produce distinct and peculiar cases of human infections [9, 10]. The distribution of the parasite varies widely globally, with *Plasmodium falciparum* responsible for 95% of infection and death from severe malaria and malaria-related complications in sub-Saharan Africa [9].

According to the latest global malaria report by the World Health Organization released in December 2021, an estimated 69 000 more people died from malaria in 2020 compared to

2019 (627 000 vs. 558 000) (WHO, 2021). [81]. This report by the world health organization showed that despite numerous combative efforts against the parasite, malaria continues to be a major burden causing morbidity and mortality, particularly in Africa and Asia affecting mostly children under 5 years of age. In addition to emerging drug-resistant isolates against first-line agents (the artemisinin), recent reports on the increase in virulence of *P. vivax*, *P. knowlesi*, and *P. malariae* resulting in severe malaria further signal impending future difficulties in the fight against the parasite [12, 13]. Thus, it is imperative to explore the relationship between malarial pathogenesis and newly discovered regulated cell death mechanisms such as ferroptosis which could serve as a novel target in drug screening and development efforts.

1.2 Ferroptosis

This is a newly discovered iron-dependent lipids peroxidation-driven cell death distinct in morphology, biochemistry, and genetics from classical cell deaths such as apoptosis, necrosis, and other non-apoptotic programmed cell deaths. Ferroptosis was first described by Dixon *et al*. in 2012 and the first usage of the term ferroptosis to refer to this type of cell death [14]. Ferroptosis occurs when polyunsaturated lipid reactive species burden overwhelms the cell's defense mechanisms against such oxidative stress. Central to this defense mechanism is glutathione peroxidase 4 (GPX4) which works both in the cytosol and mitochondria, the ubiquinol-ferroptosis suppressor protein 1 (FSP1) system which works along with cytosolic GPX4 and the ubiquinol-dihydroorotate dehydrogenase system which works along with mitochondrial GPX4. Failure of these systems to contain membrane lipids peroxidation results in membrane damage and cell death [15]. Unlike apoptosis which can be triggered by normal metabolic processes of the cell, ferroptosis is more associated with response to internal stressors such as oxidative stress and various types of metabolic imbalances without the involvement of pro-death proteins, a form of "sabotage" rather than a pro-active conscious "suicide" mechanism [16].

Ferroptosis is currently being explored to design clinical interventions for cancer and neurodegenerative diseases (references). It has also been discovered to be an important mechanism of action underlying the therapeutic effects of many drugs. Numerous compounds currently being used as drugs have been identified as ferroptosis modulators [17]. Although research related to this form of cell death has been on the increase since 2012 (**Fig 1.2A**), very little has been done to explore its role in the pathogenesis of malaria **(Fig 1.2B)**.

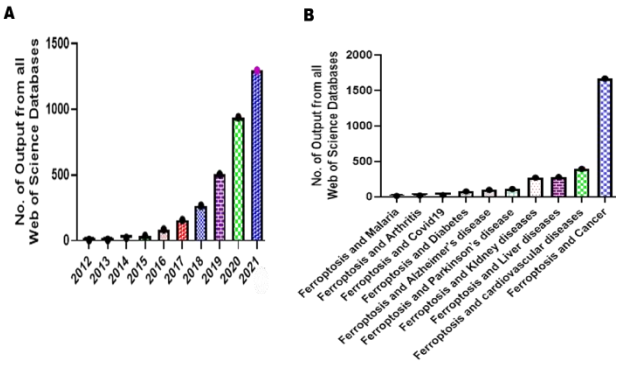

Fig 1.2 Search result for (A) "ferroptosis" (topic search) and (B) "ferroptosis and X" where X stands for a particular disease (topic search) from the web of Science database. The search was conducted on the 5th of October, 2021.

1.3 Pathogenesis of Malaria

The development of malaria from infection to death is yet to be fully elucidated. However, substantial progress has been made over the past decades in understanding the various biochemical, genetic, and physiological hallmarks implicated in the onset and progression of the disease. Red blood cell destruction and parasite adherence to vasculature endothelium presently serve as the major events in malaria pathogenesis [18]. Most of the things known about malaria pathogenesis were studied in the most important human parasite Plasmodium falciparum [19]. Given that, this section on malaria pathogenesis applies directly to P. falciparum unless otherwise stated.

P. falciparum is an obligate human malarial parasite with no recorded incidence of infecting other species [20]. Plasmodium falciparum malaria has three major clinical presentations: abnormalities within the nervous system, severe anaemia, and respiratory distress [23]. P. falciparum's life cycle involves two hosts: the female Anopheles mosquito and the human host. Female Anopheles mosquito during a blood meal injects saliva containing sporozoites into the bloodstream of its victim. Also, transmission can occur occasionally during blood transfusion and/or from mother to child [21]. Sporozoites that made it to the blood capillaries from the dermis travel to the liver where they multiply asexually for 7-10 days in a process known as schizogony, the matured forms known as liver schizonts are subsequently released in the form of merozoites into the bloodstream. Sporozoite entry and development in hepatocytes is a clinically asymptomatic event [22]. The released merozoites infect erythrocytes where they undergo repeated cycles of development and replication after which the infected red blood cells burst and release more merozoites which in turn infect other red blood cells and the cycle continues [23]. Destruction of the red blood cells is responsible in part for the classical clinical symptoms of fever, chills, and anaemia usually seen in the first stage of the disease. It also confers to malaria, a multi-organ complication because all body organs depend on the red blood cells for the supply of oxygen [24]. Plasmodium glycosylphosphatidylinositol (GPI) also known as the malaria toxin has been shown to trigger excessive production of pro-inflammatory cytokines; tumour necrosis factor α (TNF-α),

interferon γ (IFN-γ), and interleukins by the immune system following infection. These cytokines and others result in a general systemic inflammatory response with accompanying classical initial symptoms of infection including fever, chills, nausea, and vomiting [25] and are also responsible for malaria-associated lactic acidosis, hypoglycemia and, end-organ damage [26, 27].

The liver stage forms of P. vivax and P. ovale can enter into dormant forms known as hypnozoites that can remain for months and years before reactivation. This results in relapse and poses a major challenge in the treatment of infection caused by these parasites, [28]. Another unique feature of *P. vivax* infection is the use of the Duffy antigen for preferential entry into reticulocytes rather than matured red blood cells [29]. These partly explain why the parasite rarely causes infection in Africans who predominantly lack the Duffy antigen and low virulence due to its selective infection of reticulocytes. Stages in the parasite's life cycle vulnerable to ferroptosis have been highlighted in Figure 1.3.

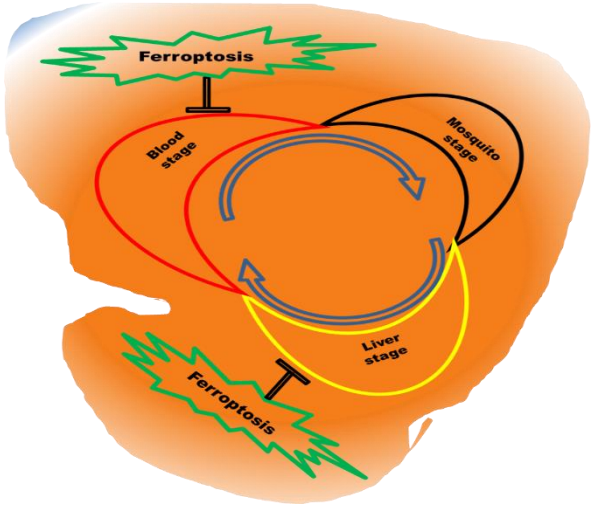

Fig 1.3 Stages in the life cycle of plasmodium targetable by ferroptosis

2.0 Indicators of a Link between Malaria and Ferroptosis

2.1 Artemisinin Mechanism of Action

The mechanism underlying the toxicity of artemisinin against plasmodium has been extensively studied. However, there are still some grey areas that need to be resolved (Reference). The prevailing theory is that of haem-mediated activation of the artemisinin molecule by the cleavage of its endoperoxide ring which results in free radicals generation and promiscuous attack on parasite proteins and other macromolecules [30, 31]. The Ca2+ transporter PfATP6 was identified using computational analysis as a potential key player in the artemisinin mechanism of action [32]. In another study, the unfolded protein response pathway is thought to play a role in its mechanism of action [33]. In addition, the enzyme inhibition activity of P. falciparum phosphatidylinositol-3-kinase by artemisinin has been reported [34]. These findings suggest that other possible mechanisms exist to complement the classical haem-endoperoxide free radical generation hypothesis. Although the contribution of ferroptosis to arteminisin's mechanism of action against malaria has not been reported, several studies have implicated ferroptosis as the force behind its anti-tumour activity (reference). Reported mechanisms through which artemisinin and its derivatives induce ferroptosis in tumours include the inhibition of glutathione peroxidase 4 (GPX4), autophagy-dependent degradation of ferritin [35] and ChaC glutathione-specific gamma-glutamylcyclotransferase 1 (CHAC1) expression induced by unfolded protein response [36]. In view of the finding by Mok et al., [33] implicating unfolded protein response in parasite resistance to artemisinin, its role in ferroptosis modulation in non-cancerous, plasmodium-infected cells need to be investigated.

2.2 Involvement of Oxidative Stress in the Pathogenesis of Malaria

Oxidative stress occurs in the cell when there is an imbalance between factors that increase the proliferation of oxidants such as infection or medication and the cell's antioxidant defense capacity [37]. When that happens, excess free radicals attacks and destroy numerous macromolecules thus resulting in the pathogenesis of many diseases. Oxidative stress is a major player in the pathogenesis of malaria. It is responsible in part for damaging the red blood cells, vital body organs, the immune system, and the parasite [38]. Oxidative stress is a well-established concept in malaria pathogenesis resulting partly due to parasite digestion of haemoglobin which releases free amino acids and iron-rich haem moiety [39]. Increased iron levels in the cell could drive the Fenton reaction, producing the highly toxic hydroxyl radical that can overwhelm the infected red blood cell and parasite antioxidant defences. Furthermore, immune system responses against plasmodial infection result in the generation of ROS [40]. Many studies have shown that oxidative stress biomarkers are significantly higher in malaria-infected than non-infected humans and mice models [40, 41]. The role of oxidative stress in malaria pathophysiology is not clear as some studies showed it has a protective role while others showed it is implicated in the disease pathophysiology [42, 43]. This could be a result of the susceptibility of both parasite and host to oxidative stress-mediated damage. However, since the current first-line antimalarial agents, the artemisinin, act via free radical-mediated damage to parasites and infected red blood cells, oxidative stress could play a protective role against malaria.

Parasite-mediated increases in lipids peroxidation decreased levels of vitamin C, and GSH were reported as important drivers of oxidative stress in malaria infection [44, 45]. Some studies have reported that the anti-oxidant capacity of erythrocytes is modulated by Plasmodium infection. In a study involving human subjects infected with P. falciparum and P. vivax, it was found that the level of superoxide dismutase and catalase significantly decreased while that of malondialdehyde, a ferroptosis marker significantly increased [46]. Also, deficiency in glucose-6-phosphate dehydrogenase (G6PD), a key enzyme in the erythrocyte antioxidant enzyme system has been reported to confer resistance against malaria [47]. This further suggests that biochemical changes that affect oxidative stress and possibly, ferroptosis could affect disease progression. An adequate understanding of how oxidative

stress affects both parasite and host could facilitate the development of rationally designed drugs that selectively target the parasite.

As a survival strategy, Plasmodium arms itself with a robust anti-oxidant enzyme system which primarily consists of the glutathione and thioredoxin systems [48]. This is necessary given that its life cycle involves close interaction with iron in a highly oxidizing environment. It is important to note that central to ferroptosis inhibition is the GPX4-GSH system which protects membrane lipids from oxidation. Accumulating evidence revealed that *Plasmodium* has an efficient system for the production of GSH and can even supply the host erythrocyte. In a study conducted to assess the export of glutathione from human erythrocytes and P. falciparum [49], it was discovered that the parasite export GSH into the host erythrocyte's cytoplasm even under oxidative challenge. Glutathione has been implicated in artemisinin resistance in kelch13-mutant P. falciparum [50] and the response of P. berghei to chloroquine and artemisinin [51]. Glutathione-S-transferases (GSTs) are a group of GSH-dependent enzymes found in Plasmodium and are known to possess a selenium-independent glutathione peroxidase activity towards organic hydroperoxides [52]. These enzymes could be involved in the detoxification of peroxidised membrane phospholipids and ferroptosis inhibition in the parasite.

The glutathione peroxidase gene in P. falciparum codes for an enzyme that reacts faster with thioredoxin than with GSH and unlike mammalian glutathione peroxidase was unable to neutralize phosphatidylcholine hydroperoxide [53]. The enzyme is therefore regarded as a thioredoxin peroxidase. To facilitate the production of NADPH which serves as reducing power for GSSG, Plasmodium has an efficient pentose phosphate pathway with a pfG6PD enzyme having some molecular differences from its mammalian counterpart (hG6PD). In the substrate-binding site of pfG6PD, Arg365 in hG6PD has been replaced by Asp750 [54]. This makes it a good target for selectively inducing ferroptosis in the parasite. However, other reports ascribed the production of NADPH in P. falciparum to the activity of glutamate dehydrogenase [55]. The membrane phospholipid hydroperoxide detoxification system of Plasmodium may be central to its ferroptosis susceptibility and hence needs to be fully elucidated.

2.3 The Role of Vitamin E in Malaria Pathophysiology

Vitamin E (α-tocopherol) is a major lipid-soluble non-enzymatic component of the cell's antioxidant system responsible for protecting the cell membrane against lipid peroxidation [56]. The role of vitamin E in the pathophysiology of malaria appears to be both protective and harmful depending on several factors [57]. Studies have shown that the malarial parasite uses vitamin E to protect itself from oxidative stress that accompanies the disease [58]. Vitamin E deficient murine models of malaria infection showed decreased resistance to an increase in parasitemia [59]. Other groups argue that the antioxidant properties of vitamin E could serve a general purpose in reducing organ damage resulting from malaria-induced oxidative stress [60]. Vitamin E was found to antagonize the antimalarial effect of artemisinin [61]. Also, Herbas et al [62] reported that inhibition of α-tocopherol transfer protein (α-TTP) acts synergistically with the oxidative stress-inducing antimalarial drug- chloroquine, and such interaction can be exploited to optimize the therapeutic effect of anti-malarial agents. These studies showed that vitamin E interacts with antimalarial agents via oxidative stress-related mechanisms. Vitamin E might be involved in blocking iron-catalyzed lipid peroxidation of both parasite and host membrane lipids. Unless parasite and host response to oxidative stress is fully understood, and strategies designed to selectively protect the host while targeting the parasite, any attempt to use oxidative stress induction as a clinical intervention in malaria may be counterproductive.

2.4 Membrane Lipids Composition of *P. falciparum* and P. falciparum-infected Erythrocytes

A study conducted to evaluate the modification of host erythrocyte membrane by Plasmodium revealed that the level of phosphatidylcholine and phosphatidylinositol were higher in P. falciparum-infected erythrocytes than in uninfected ones while sphingomyelin levels were higher in non-infected erythrocytes [63]. These authors also reported a large increase in the level of palmitic acid and oleic acid in infected erythrocytes with a corresponding major decrease in the level of arachidonic acid, docosahexaenoic, and other polyunsaturated fatty acids. The fatty acid profile of infected erythrocytes shows more resemblance to that of Plasmodium than the uninfected erythrocytes suggesting parasite-mediated modification of infected erythrocyte membrane phospholipid composition [64].

A significant decrease in the amount of erythrocyte membrane polyunsaturated fatty acids PUFA from 39.4% to 24% as reported in this study [64] could result in the inhibition of ferroptosis in the parasite. Another study reported that the lipid composition of an infected erythrocyte changes as the parasite transits from one developmental stage to another [65]. These changes could be a result of the parasite's adaptation to changing pro-ferroptotic microenvironment. Lipid biosynthesis has also been reported to be elevated during the erythrocytic stages of the parasite life cycle [66]. Decanoic acid, lauric acid, and myristic acid are the major components of P. falciparum membrane fatty acids [67]. These fatty acids are all saturated and therefore resistant to ROS-mediated peroxidation. By mobilizing saturated fatty acids on its membrane, plasmodium will become more resistant to membrane phospholipids-related oxidative stress. This is particularly important given that parasite metabolism in the red blood cell releases heme which can catalyse the Fenton reaction [68]. The PUFA composition of infected erythrocytes membrane is altered by the parasite in a manner that makes it resistant to ferroptosis. The parasite might have induced those changes to protect the erythrocyte membrane from premature ferroptosis-mediated rupture. Premature destruction of the erythrocyte membrane could result in the release of immature gametocytes and merozoites which may not have the ability to infect surrounding erythrocytes nor survive in the mosquito's mid-gut thereby ending the parasite's life cycle.

2.5 Anti-plasmodial Activity of Polyunsaturated Fatty Acids (PUFAs)

Several studies have demonstrated the anti-plasmodial activity of fatty acids both in vitro and in vivo. The work of Kumaratilake et al [69] revealed that polyunsaturation is an important factor in the antiplasmodial effect of fatty acids where docosahexanoic acid demonstrated potent activity against the parasite with more than 90% death at a concentration of 20-40 µg//mL. According to the authors, lipid peroxidation was a plausible mechanism for the observed fatty acid antiplasmodial effect. Polyunsaturation and lipids peroxidation was later reported as not necessary for fatty acid antiplasmodial activity though the authors here did not propose an alternative mechanism [70]. Murine C23–C26 Δ5,9 fatty acids were shown to be potent inhibitors of P. falciparum enoyl-ACP reductase (FabI) enzyme that catalyses the final reduction step of the fatty acid chain elongation cycle in P. falciparum [71]. It is therefore conceivable that fatty acids could inhibit P. falciparum lipid biosynthetic pathways thus making them potential therapeutic agents. However, this could be a feedback inhibition since the polyunsaturated fatty acids that need to be synthesized have been exogenously supplied. In another study, human phospholipid-derived PUFAs were shown to possess significant in-vitro anti-plasmodial activity [72].

2.6 Susceptibility of Trypanosome to Ferroptosis/Ferroptosis-mediated Killing of *Plasmodium* at the Liver Stage

Previous studies have revealed that trypanosomes deficient in tryparedoxin peroxidase undergo ferroptosis [73]. This enzyme performs the same biochemical function as mammalian GPX4. Given that both trypanosome and plasmodium are protozoans, inhibiting plasmodium peroxidase enzymes could also induce ferroptosis. A recent study has shown that ferroptosis plays an important role in eliminating liver-stage Plasmodium yoelii. Kain et al discovered that genetic or pharmacological disruption of the host GPX4-SLC7a11 signaling pathway results in a significantly lower parasitemia in the liver of infected mice [74]. They observed an extensive lipid peroxidation on the parasite cell membrane in response to treatment with erastin, a SLC7a11 inhibitor that induces ferroptosis. This was found to diminish in NADPH oxidase 1 or transferrin receptor 1 knockdown controls. It was earlier reported that p53 is involved in parasite clearance in the liver of Plasmodium yoelii infected mice through a non-apoptotic cell death mechanism therefore; its inhibition is required for *Plasmodium* liver-stage infection [75]. Kain et al established that the p53-mediated non-apoptotic cell death mechanism involved in killing plasmodium at the liver stage is ferroptosis. This finding is of special interest to Africans and people of African descent because of the discovery of an African-specific single nucleotide polymorphism (SNP) at codon 47 of the human p53 gene which results in the replacement of serine residue with proline. This polymorphism has compromised p53's role in ferroptosis induction [76]. The newly discovered contribution of host ferroptosis to the reduction of liver-stage parasite load means that this polymorphism could be a contributing factor to the high malaria burden in Africa. However, a recent study revealed that this polymorphism could confer an advantage against malaria through the generation of an altered macrophage phenotype that is less sensitive to the malaria toxin, hemozoin [77]. This reported advantage could only reduce the severity of the symptoms and not parasite viability.

In another study that investigated the effect of dietary alterations on host susceptibility to plasmodium infection, it was discovered that the administration of a high-fat diet to mice for 4 days impairs Plasmodium liver stage infection by over 90% [78]. The study revealed that plasmodium sporozoites die inside the hepatocytes after a successful invasion. A probe into the mechanism of action implicated oxidative stress, as the effect was obliterated by the antioxidant, N-acetylcysteine. Although this study did not specifically assess the contribution of a high-fat diet to ferroptosis, this iron-dependent cell death has not been ruled out. The possible involvement of ferroptosis is supported by an earlier study that reported the inhibition of heme synthesis which increases hepatic labile iron pool, to result in the inhibition of liver-stage parasite development [79]. The link between malaria and ferroptosis has been highlighted in **Fig 2.**

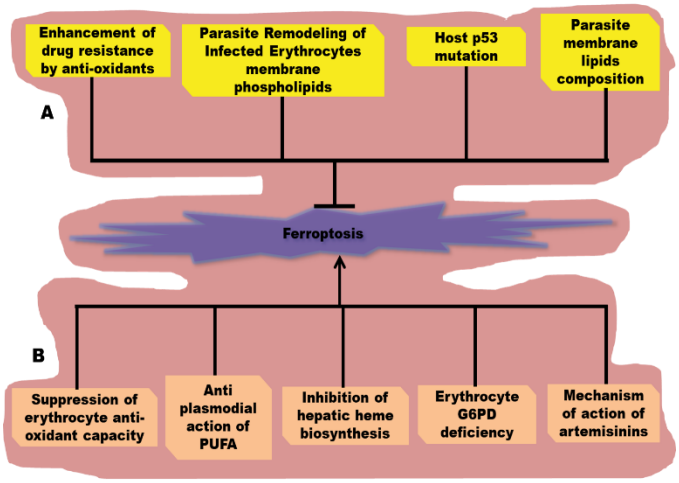

Fig 2 (A) Processes associated with the inhibition of ferroptosis in the pathogenesis of malaria (B) Processes associated with the induction of ferroptosis in the pathogenesis of malaria

3.0 Conclusion and Future Perspective

Ferroptosis could affect the pathogenesis of malaria either through parasite elimination or the destruction of infected red blood cells or liver cells. While parasite clearance could halt disease progression, excessive destruction of host cells could result in unwanted adverse events. Plasmodium-mediated increase in cellular haem concentration via hemoglobin degradation could drive Fenton reaction resulting in the production of excess lipid hydroperoxides. This may overwhelm parasite antioxidant defenses leading to cell death by ferroptosis. The parasite responds to this putative ferroptosis-mediated death threat by converting toxic haem to hemozoin and changing the lipid composition of membranes from ferroptosis susceptible to ferroptosis resistant. It is also possible that the parasite, especially at the blood stage, activates other biochemical pathways that make it less

susceptible to ferroptosis. This iron-dependent cell death could be a major contributor to the mechanism of action of artemisinins. Ferroptosis was described just recently and its role in malaria parasite biology and pathogenesis has not been explored [80]. This review has revealed an important link between malaria and ferroptosis. We, therefore, recommend conducting research towards unraveling the relationship between malaria infection dynamics, antimalarial drug's mechanism of action, and this regulated cell death. Ferroptosis research in malaria could open up a new chapter in understanding the disease pathogenesis, antimalarial mode of action, mechanism of drug resistance and provide molecular targets for the development of novel antimalarial agents. As a result of the implication of ferroptosis in the pathogenesis of many diseases, several ferroptosis-associated biochemical pathways in eukaryotes have been identified. Most of these pathways are related to the cell antioxidant defense system, lipid metabolism, and iron homeostasis. These include metabolic pathways associated with reduced glutathione, PUFAs, ubiquinol, iron import, storage, and export. Identification of parasite equivalent of human ferroptosis-associated biochemical pathways could open new avenues for selectively inducing ferroptosis in the parasite while sparing the host. If ferroptosis is fully exploited, the life cycle of plasmodium could be effectively arrested at the blood stage.

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