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BIOMEDICAL SCIENCES

Lycopene supplementation promoted increased survival and decreased parasitemia in mice with severe malaria: comparison with N-acetylcysteine

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Abstract: Oxidative stress is involved in the pathogenesis of malaria, causing anemia, respiratory complications, and cerebral malaria. To mitigate oxidative stress, we investigated the effect of nutritional supplementation whit lycopene (LYC) on the evolution of parasitemia and survival rate in mice infected with *Plasmodium berghei* ANKA (Pb), comparing to the effects promoted by N-acetylcysteine (NAC). Therefore, 175 mice were randomly distributed into 4 groups; ***Sham*:** untreated and uninfected animals; **Pb**: animals infected with Pb; **LYC+Pb:** animals treated with LYC and infected with Pb; **NAC+Pb**: animals treated with NAC and infected with Pb. The animals were followed for 12 days after infection, and survival and parasitemia rates were evaluated. There was a 40.1% increase in parasitemia in the animals of the Pb group on the 12th day, and a survival rate of 45%. LYC supplementation slowed the development of parasitemia to 19% and promoted a significative increase in the survival rate of 80% on the 12th day after infection, compared to the Pb group, effects superior to those promoted by NAC, providing strong evidence of the beneficial effect of LYC on *in vivo* malaria and stressing the importance of antioxidant supplementation in the treatment of this disease.

Key words: Antioxidants, oxidative stress, Lycopene, malaria, N-acetilcysteine.

INTRODUCTION

Malaria is a serious global public health problem with a significant number of cases in 2020, when some 241 million cases occurred and 627,000 people died as a result of this disease. Currently, malaria is endemic in 85 countries, mainly in tropical and subtropical areas, where it mainly affect poor communities, especially pregnant women and children, and causing devastating social and economic consequences (WHO 2021).

Plasmodium vivax is the most commonly malaria-causing *Plasmodium* species in the world and is implicated in relapses of the disease (Angrisano & Robinson 2022, Rougeron et al. 2022). *P. falciparum* is recognized as the main cause of severe forms of the disease, being the most lethal species (Howes et al. 2016, Pais et al. 2022).

Some factors have been implicated in the pathogenesis of malaria, but one of the key processes contributing to the severity of the disease is excessive production of reactive oxygen and nitrogen species (RONS) in the host organism (Moreira et al. 2021, Gomes et al. 2022), Indeed, RONS can impact antioxidant defenses, promoting important cellular damage, including the reduction of red blood

cell deformability causing consequent hemolysis, metabolic acidosis, severe anemia, and cerebral malaria (Haldar et al. 2007, Srivastava et al. 2015, Kumar et al. 2018). Ultimately, it may lead to the death of the host (Quadros Gomes et al. 2015, Barbosa et al. 2021).

Studies have found that populations in malaria endemic areas are more susceptible to complications of the disease, especially those caused by *P. falciparum*, because they have low plasma concentrations of several micronutrients important for host-defense mechanisms, including vitamin A and zinc, in addition to antioxidants such as ascorbic acid (vitamin C), vitamin E (α-tocopherol) and carotenoids such as lycopene (LYC) and β-carotene (Adelekan et al. 1997, Nussenblatt et al. 2002).

Among carotenoids, LYC stands out a potent mobilized antioxidant, which has been shown to reduce oxidative stress and prevent excessive production of RONS, especially those involved in malaria (Miller et al. 1996, Anguelova & Warthesen 2000). LYC is an essential micronutrient for living organisms, and its primary source is photosynthetic organisms, including green plants, algae, and cyanobacteria, being found in greater quantity in tomatoes and derivatives (Cohn et al. 2004, Wang et al. 2020).

LYC has analogues, including *cis* and *trans* isomers and apo-lycopenols, such as apo-10'-lycopenoic acid (Lian & Wang 2008, Rodriguez & Rodriguez-Amaya 2009, Reynaud et al. 2011). Both isomers are non-cyclic liposoluble hydrocarbons with saturated and unsaturated lateral chains, which offer greater reactivity with RONS (Novikov et al. 2022). These carotenoids have potent activities, including antioxidant (Sy et al. 2012, Catalano et al. 2013), anti-inflammatory (Feng et al. 2010, El-Ashmawy et al. 2018), anticancer (Aust et al. 2003, Cheng et al. 2020), cardioprotector (Ferreira-Santos et al. 2018), hepatoprotector (Ni et al. 2020), nephroprotector (Karahan et al. 2005), neuroprotector (Yin et al. 2014, Paul et al. 2020), antidiabetic (Guo et al. 2015), anticataract (Mohanty et al. 2002), and cholesterol reduction (Renju et al. 2014), being more potent than β-carotene or α-tocopherol (Liu et al. 2008, Erdman et al. 2009).

Additionally, a significant antiparasitic effect of LYC has been reported in experimental infection with *P. falciparum in vitro* (Agarwal et al. 2014). Other studies suggest that treatment with antioxidants may improve antiparasitic immune response (Val et al. 2015, Dkhil et al. 2019). However, it is unclear whether LYC stimulating actions demonstrated in *in vitro* studies, such as RONS inhibition and apoptosis induction, may occur in *in vivo* malaria.

Thus, this is the first study to clarify whether LYC is an appropriate candidate to antimalarial adjuvant, capable of reducing oxidative stress in male Balb/c mice infected with *P. berghei* ANKA, a murine malaria strain, responsible for inducing in mice a syndrome similar to that caused by *P. falciparum* in humans, and that it is well characterized in regards of the involvement of oxidative mechanisms in its pathophysiology.

MATERIALS AND METHODS

We used 175 male mice of the species *Mus musculus* and Balb/c breed, adults, 7-10 weeks old, weighing between 25 and 40g, from the Vivarium of the Evandro Chagas Institute (Ananindeua, Pará-Brazil). The animals were housed in the Experimental Vivarium of the Oxidative Stress Research Laboratory (LAPEO) of the Institute of Biological Sciences (ICB) of the Universidade Fededral do Pará (UFPA), at room temperature of 24±2°C, light/dark cycle of 12 hours (lights from 7:00h to 19:00h), and

free access to food and water. Before any experimental procedure, the animals were acclimated to laboratory conditions for 15 days.

The project was approved by the Ethics Committee on the Use of Experimental Animals of UFPA (CEUA/UFPA; protocol 3235130919), and the animals were manipulated and cared for in accordance with the ethical standards of animal experimentation set forth by the Brazilian Society of Laboratory Animal Science.

Preparation and administration of lycopene and N-acetylcysteine

The LYC administration protocol was chosen based on a dose-response study on the effects of LYC supplementation on oxidative stress biomarkers (Devaraj et al. 2008), and the dose was calculated by allometric extrapolation (Nair & Jacob 2016). The animals received 3.11mg/kg b.w./day of LYC *via* gavage (Table I).

The N-acetylcysteine (NAC) administration protocol was chosen based on a randomized, double-blind, placebo-controlled study of chronic obstructive pulmonary disease (Zheng et al. 2014) and the dose was calculated by allometric extrapolation (Nair & Jacob 2016). The animals received 62mg/kg b.w./day of NAC *via* gavage (Table I).

The antioxidant drug NAC has been proposed as adjunctive treatment in severe falciparum malaria both *in vitro* and *in vivo* studies (Watt et al. 2002, Treeprasertsuk et al. 2003, Arreesrisom et al. 2007, Quadros Gomes et al. 2015) and, therefore, was employed as standard in this study.

Treatment with both substances was started 24 hours before infection of the animals with *Plasmodium berghei*, being repeated every 24 hours, until the day before the euthanasia of the animals.

Table I. Method for the calculation of allometric extrapolation of doses to be administered to mice (Balb/c, body weight of 0.025 kg).

A: dose calculation by allometric extrapolation – Lycopene	B: dose calculation by allometric extrapolation – N-acetylcysteine
Basal Metabolic Rate of reference animal (BMR man): BMR man = k x $m^{0.75}$ = 70 x $70^{0.75}$ = 70 x 24.20 BMR man = 1.694 kcal **BMR of target animal (BMR mice):** BMR mice = k x $m^{0.75}$ = 70 x $0.025^{0.75}$ = 70 x 0.063 BMR mice = 4.4 kcal **Total Dose indicated in the literature (TD):** TD = DOSE man ÷ BMR man = 30 ÷ 1.694 TD = 0.0177 mg/kcal **TD of the target animal (TD mice):** TD mice = TD x BMR mice = 0.0177 x 4.4 TD mice = 0.077 mg of Lycopene Therefore, the total dose of lycopene indicated to one mouse of 0.025 kg is 0.077 mg (or 3.11 mg/kg), which was administered every 24 h.	BMR man: BMR man = k x $m^{0.75}$ = 70 x $70^{0.75}$ = 70 x 24.20 BMR man = 1.694 kcal **BMR mice:** BMR mice = k x $m^{0.75}$ = 70 x $0.025^{0.75}$ = 70 x 0.063 BMR mice = 4.4 kcal **TD:** TD = DOSE man ÷ BMR man = 600 ÷ 1.694 TD = 0.354 mg/kcal **TD mice:** TD mice = TD x BMR mice = 0.354 x 4.4 TD mice = 1.55 mg of N-acetylcysteine Therefore, the total dose of N-acetylcysteine indicated to one mouse of 0.025 kg is 1.55 mg (or 62 mg/kg), which was administered every 24 h.

A: Taking as reference the adult man (*Homo sapiens*; average weight of 70 kg; proposed lycopene dose = 30 mg) is taken as reference. B: Taking as reference the adult man (*Homo sapiens*; average weight of 70 kg; dose of N-acetylcysteine proposed = 600 mg). k = constant of large taxonomic groups (placental mammals = 70); m = body mass.

Malaria induction

The *Plasmodium berghei ANKA* (Pb) strain was originally supplied by the Evandro Chagas Institute (Ananindeua, Pará-Brazil). For the infection, $1x10^6$ red blood cells infected *by P. berghei* ANKA were injected intraperitoneally (i.p.) into mice, and their survival and parasitemia rates were monitored. The day of infection was defined as day 0.

Animals and experimental groups

175 mice were randomly distributed into 4 groups (Figure 1), including: ***Sham*** (n=28): mice that received just the vehicle (water; gavage) and non-parasitized red blood cells (i.p.); **Pb** (n=49): mice that received just the vehicle (water; gavage) and Pb-infected red blood cells (i.p.); **LYC+Pb** (n=49): mice treated with 3.11mg/kg b.w./day of LYC (gavage) and infected with Pb (i.p.); **NAC+Pb** (n=49): mice treated with 62mg/kg b.w./day of NAC (gavage) and infected with Pb (i.p.). Each group was subdivided into 4 subgroups, depending on the number of days of follow-up of the group, and the animals of these subgroups underwent euthanasia after 1, 4, 8, or 12 days after infection.

Due to the high mortality expected for the subgroups of animals with longer infection periods (groups Pb, LYC+Pb, and NAC+Pb), their subgroups 1 and 4 days were composed of 7 animals each. Subgroups 8 and 12 days consisted of 15 and 20 animals, respectively. Since they would not undergo infection, all subgroups of the ***Sham*** group consisted of 7 animals.

Determination of survival rate

At the end of the period of 1, 4, 8 and 12 days, the survival rate was calculated by equation 1:

$$\text{Survival rate (\%)} = \frac{\text{number of infected animals alive at the end of the study}}{\text{total number of infected animals alive at the begining ot the study}} \times 100 \quad (1)$$

Determination of parasitemia

At the end of the period of 1, 4, 8, or 12 days, 30µL of blood was collected by puncture of the caudal vein to produce blood smears, which were fixed with methanol (Dynamics, Cat # 1230) and stained

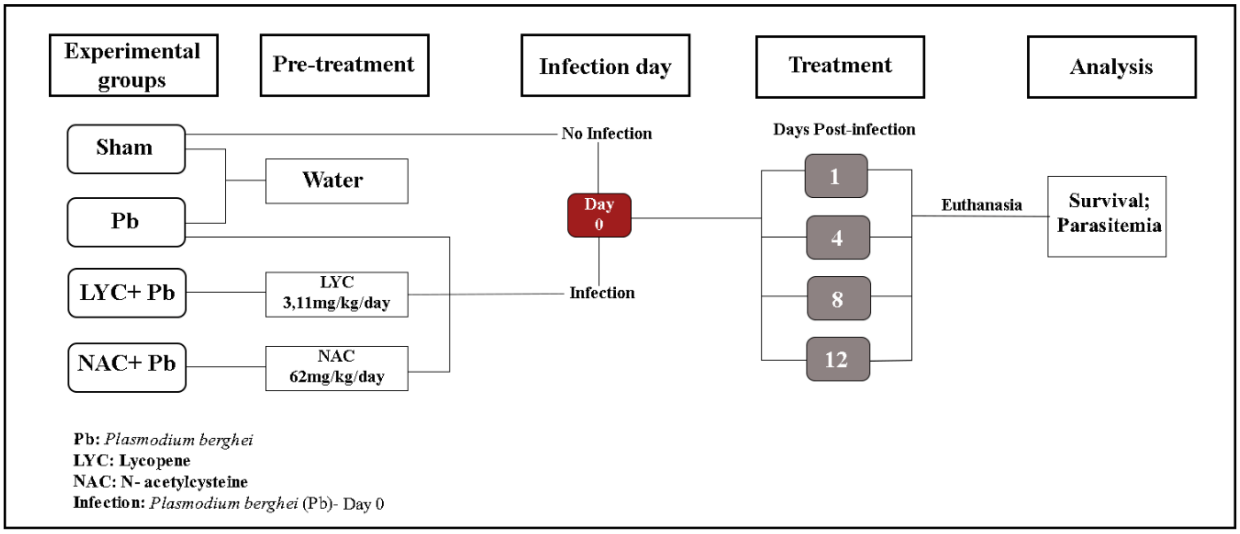

Figure 1. Schematic representation of the experimental design. LYC: Treatment with lycopene; NAC: Treatment with N-acetylcysteine.

with Giemsa (10%; Merck, Cat #1092041022). Parasitemia was determined by cell counting using the optical microscope (1000X), allowing to evidence the presence of the parasite within red blood cells. After counting, the percentage of parasitemia was calculated using equation 2:

$$\text{Parasitemia (\%)} = \frac{\text{number of infected erythrocytes}}{\text{total number of erythrocytes}} \times 100 \quad (2)$$

Statistical analysis

Data were expressed as mean ± standard deviation. All data were compared and analyzed using the one-way Variance Analysis test (ANOVA). Significant differences were compared between the groups, through Tukey's *post-hoc* test. In all tests, a significance level of 5% was considered ($p \leq 0.05$).

RESULTS

Effect of lycopene on survival rate

The survival rate of Pb group animals decreased from 100% on the 4th day to 46.7% on the 8th day after infection, and on the 12th day after infection it further decreased to 45%. On the other hand, animals treated with NAC presented a survival rate of 93.3% and 70% on days 8 and 12 post-infection, respectively, higher than the animals of the Pb group on the same days (p<0.0001). Additionally, animals treated with LYC exhibited a survival rate of 80% on both days 8 and 12 post-infection. In addition, LYC increased the survival of the animals significantly (p<0.0001) in relation to Pb group on days 8 and 12 post-infection and NAC+Pb group, on day 12 post-infection (Figure 2).

Effect of lycopene on the progression of parasitemia

Figure 3 shows the evolution of parasitemia in the Pb, LYC+Pb, and NAC+Pb groups. Parasitemia progressively evolved in all groups, but the rate of progression was significantly lower in animals treated with LYC during the study period (p<0.0001). In addition, the animals treated with LYC showed a significant reduction in parasitemia (p<0.0001), in relation to the Pb group on days 4, 8, and 12 post-infection and NAC+Pb group on day 12 post-infection (Figure 3).

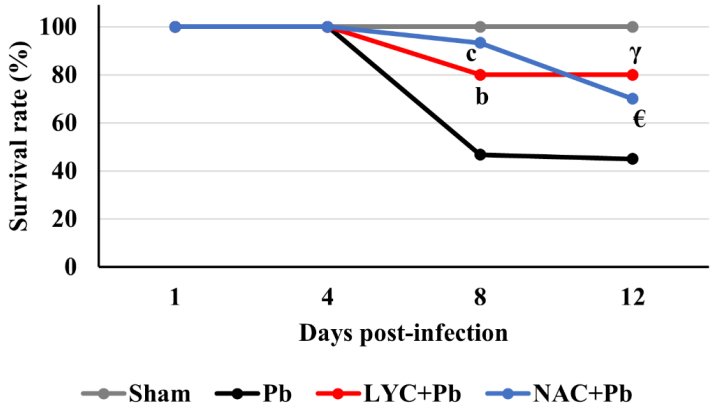

Figure 2. Survival rate of Balb/c mice infected with *Plasmodium berghei* ANKA treated with lycopene (LYC) or N-acetylcysteine (NAC). The ANOVA test, followed by Tukey's *post-hoc* test, was used to compare the Shan, Pb, LYC+Pb and NAC+Pb groups. ^{b}p<0.0001 *versus* Pb group and NAC+Pb; ^{c}p<0.0001 *versus* Pb group; $^{\gamma}p$<0.0001 *versus* Pb group and NAC+Pb; $^{€}p$<0.0001 *versus* Pb. Sham group: untreated and uninfected animals; Pb: animals injected (i.p.) with 10^6 red blood cells infected with Pb; LYC+Pb: animals treated with 3.11 mg/kg b.w./day of lycopene and infected with Pb; NAC: animals treated with 62 mg/kg b.w./day of NAC and infected with Pb.

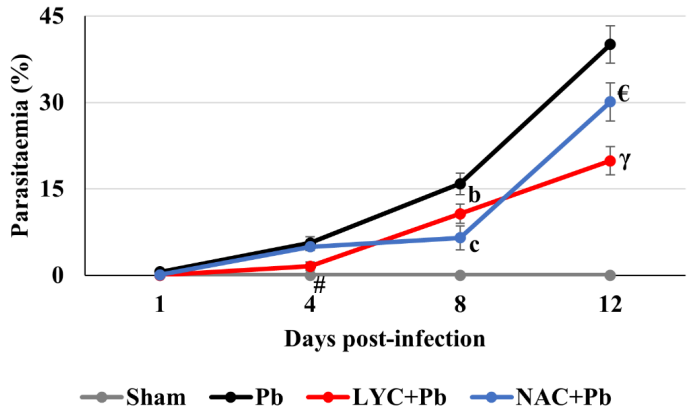

Figure 3. Temporal evolution of parasitemia of Balb/c mice infected with *Plasmodium berghei* ANKA (Pb) and treated with lycopene (LYC) or N-acetylcysteine (NAC). The ANOVA test, followed by Tukey's *post-hoc* test, was used to compare the Pb, LYC, and NAC groups. $^{\#}p$=0.0090 *versus* Pb group; ^{b}p<0.0001 *versus* Pb group; ^{c}p<0.0001 *versus* Pb and LYC+Pb group; $^{\gamma}p$<0.0001 *versus* Pb and NAC+Pb group; $^{€}p$<0.0001 *versus* Pb. Sham group: untreated and uninfected animals; Pb: animals injected (i.p.) with 10^6 red blood cells infected with Pb; LYC+Pb: animals treated with 3.11 mg/kg b.w./day of LYC and infected with Pb; NAC: animals treated with 62 mg/kg b.w./day of NAC and infected with Pb.

DISCUSSION

Many of LYC's reported health benefits are attributed to its potent antioxidant activity, which includes effects such as cardioprotection, hepatoprotection, antidiabetc, anti-atherogenic, neuroprotective and anticancer (Duzen et al. 2019, Yin et al. 2019, Fu et al. 2020, Xue et al. 2021, Alhoshani et al. 2022, Mannino et al. 2022).

The antioxidant activity of LYC was also demonstrated in the pathogenesis of malaria in children (Das et al. 1996). Additionally, studies conducted by Agarwal et al. (2014), evidenced the *in vitro* cytotoxic effect of LYC against *P. falciparum*.

In the present study we used Balb/c mice as the vertebrate host for Pb to evaluate the effect of LYC supplementation on the evolution of parasitemia and survival in these animals.

The concentration used to evaluate the effect of LYC supplementation was chosen based on a dose-response study, which demonstrated the beneficial effects of LYC on oxidative stress biomarkers after daily intake of 6.5mg, 15mg, or 30mg of LYC (Devaraj et al. 2008). Since the daily intake of 30mg of LYC presented maximum antioxidant effect against oxidative stress, this concentration was used as a parameter for the calculation of allometric extrapolation, leading to the establishment of the LYC dose of 3.11mg/kg body weight, which was given daily until the day before euthanasia of the animals.

It was demonstrated a progressive increase in parasitemia in the Pb group during the period of 12 days after infection. In addition, a high degree of parasitemia was observed on the 12th day, reaching percentages of 40.1%. Notwithstanding, it was observed that on days 8 and 12 post-infection, 53.3% and 55% of the animals in this group died, respectively.

Additionally, the parasite count in peripheral blood may have underestimated the actual picture of parasitemia, since parasite populations may have been trapped inside microvessels of the spleen, kidneys, liver, lungs, and brain (Zaid et al. 2020), leading to lower availability of infected cells within the blood stream.

Previous studies have shown that children and adults with malaria generally have a high prevalence of malnutrition and micronutrient deficiencies, including vitamin A, β-carotene, LYC and zinc (Thurnham & Singkamani 1991, Zeba et al. 2008), and this situation creates a complexity of interactions with serious consequences for the health of the host.

According to Nacer et al. (2012), in addition to pallor, biliverdine secretion in the urine, arched posture, and lethargy, hyperparasitemia also leads to brain complications and death.

Another important factor is the exaggerated production of RONS during the disease. Pathophysiological changes in malaria escalate during the erythrocytic cycle. At this stage, parasites invade erythrocytes, consume and hydrolyse intraerythrocyte hemoglobin, seeking the amino acids for its own development (Tekwani & Walker 2005).

After the breakdown of the protein, ferrous iron (Fe^{2+}) from the released ferroprotoporphyrin can be rapidly oxidized to ferric iron (Fe^{3+}), giving rise to ferriprotoporphyrin IX, which undergoes oxidation and reduction reactions, producing RONS, such as superoxide ($O_2^{\cdot-}$), hydroxyl ($OH^{\cdot}$), nitric oxide (NO), peroxynitrite ($ONOO^{-}$), free radicals of highly reactivity (Müller 2004, Klonis et al. 2013).

Antioxidants can antagonize the deleterious effects of RONS and restore redox balance, but in malaria infection this defense is totally tampered due to the high metabolic rate of the parasite, which grows and multiplies rapidly, generating large amounts of RONS, leading to the consumption and decrease of the host's antioxidant defense system (Delhaye et al. 2016).

As a consequence of this intracellular process, there is a reduced erythrocyte deformability, which cause erythrocyte hemolysis, and additional release of RONS to extracellular medium, causing damage to other cellular structures, including membrane lipids, proteins, and DNA (Cadet et al. 2010, Rahal et al. 2014).

In the present study, animals treated with LYC showed a survival rate higher than the Pb and NAC+Pb groups on days 8 and 12 post-infection. We believe that this prophylactic activity of LYC is due to the elimination of RONS, which has been cited as a crucial factor in this stage of malaria development (Quadros Gomes et al. 2015, Al-Shaebi et al. 2018).

According to the present results, animals supplemented with LYC up to the 12th day presented the development of parasitemia at a slower rate compared to that observed in the Pb group. Moreover, LYC displayed antiparasitic potential higher than those of groups Pb and NAC+Pb in the 12th day post-infection.

Indeed, the delay in the induction and progression of parasitemia caused by treatment with LYC suggests its prophylactic and antiparasitic activity, which may be due to a cytotoxic effect of LYC against malaria parasites (Agarwal et al. 2014), as the reduction of parasitemia may be associated with increased plasma LYC concentration in these animals (Metzger et al. 2001). In fact, the lipophilic characteristic of LYC can also favor its interaction with the lipid bilayer of the cell membrane (Sy et al. 2012) facilitating its absorption in tissues such as brain, heart, liver, spleen, lung, and kidneys, preventing them from the damage caused by parasite and/or RONS (Guo et al. 2019). Therefore, antioxidants such as LYC can block the damage triggered by RONS by sharing electrons with RONS, subsequently neutralizing them (Jain et al. 2018).

Corroborating to the present results, previous studies have shown the preventive effect of LYC (10mg/kg, orally) on lipid peroxidation, oxidative damage to DNA, and on the histopathological changes in liver of animals submitted to treatment with ferric nitrilotriacetate (Matos et al. 2001). Ateşşahin et al. (2006), also stated that 10 days of treatment with LYC (4mg/kg/day) prevented cisplatin-induced lipid peroxidation in rat testicles. Moreover, data from our laboratory demonstrated that NAC supplementation to Pb-infected mice prevented the oxidative changes imposed by the

infection, suggesting that NAC may display antioxidant properties or that it is involved in redox signaling processes (Varela & Percário 2022).

In face of these results, it is possible to suggest that LYC can act in both ways: protecting against infection-induced damage, creating an antioxidant defense line in the host organism, inducing improvement of clinical parameters observed in supplemented animals, and by a direct antiparasitic effect of LYC against the parasites themselves, as suggested by Agarwal et al. (2014). Therefore, we suggest an important role of LYC supplementation both in malaria prevention and treatment.

The data obtained in the present study provide strong evidence that lycopene is effective against *P. berghei* infection and suggest that lycopene may become an important, viable, and safe strategy for the development of a biotechnological product with effective action in the prevention and auxiliary treatment of malaria and other diseases, but more studies are needed to prove these potential benefits.

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