Review

Melatonin as a microenvironmental cue for parasite development inside the host

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ABSTRACT

Throughout the evolutionary process, parasites have acquired characteristics that function as survival mechanisms. It has been reported that melatonin, a molecule present in virtually all living organisms, has several roles in parasite biology such as preventing tissue damage, regulating gene expression and inflammatory processes, and acting as a free radical scavenger. Additionally, melatonin produced by the hosts accelerates the intra-erythrocytic cycle of the human malaria parasite *Plasmodium falciparum* and the rodent malaria parasite *P. chabaudi*, respectively. These findings have recently led to an increased research enthusiasm to find how melatonin influences the biological cycle of parasites. Therefore, this review aims to gather and analyze the potential relationships of host produced melatonin with the parasites *Plasmodium sp*., *Trypanosoma cruzi*, *Leishmania spp*., *Toxoplasma gondii*, *Schistosoma mansoni*, *Opisthorchis viverrini*, and *Entamoeba histolytica*, respectively.

Key words: melatonin, parasites, pathway signaling, cAMP, analogs, malaria, receptor

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1. INTRODUCTION

Melatonin is an indolamine molecule present in almost all living organisms, from bacteria and fungi to mammals (1). The free-radical scavenger and immunomodulatory activity of melatonin have been reported over the years in a variety of biologic conditions (2, 3). The actions of melatonin as an antioxidant and modulator of immune response to protect tissue damage have been evidenced by many *in vitro* and *in vivo* studies. For example, Leite *et al.* (4) reported that melatonin treatment before intestinal ischemia-reperfusion protected the acute lung injury with the reduced oxidative stress. In diabetic rat model with the increased malondialdehyde and superoxide dismutase levels, indicative of oxidative stress, melatonin treatment was able to reverse these parameters (5). Besides its antioxidant and anti-inflammatory effects for the treatment of cancer, the influence of melatonin on apoptosis and cell proliferation processes has been studied *in vitro* with promising results (6-8). Clinically,

the use of melatonin for cancer treatments can improve the patient's outcomes concerning remission, survival and reduced side effects of the chemotherapy (9). The use of melatonin to treat respiratory viral infections also show beneficial effects. For example, melatonin treatment can reduce the symptoms and mortalities of SARS-CoV-2 infected patients (10-12)

Besides the free-radical scavenger activity, there are two melatonin receptors, MT1 and MT2, which are G-protein coupled receptors (13, 14). In mammals, the downstream signaling of melatonin involves a decrease in cyclic adenosine monophosphate (cAMP) levels (15).

Melatonin was discovered in 1958 in the bovine pineal gland (16). The pineal gland is the main source of circulating melatonin in mammals and is released into the bloodstream and cerebrospinal fluid in a light/dark circadian rhythm (17-19). The presence of melatonin synthetic pathway in other organs strongly indicates that this molecule can be produced in other parts of the body (20-22). Indeed, it has been confirmed that melatonin is produced in mitochondria, therefore, virtually every cell or system including the immune system, platelets, the gastrointestinal tract also can synthesize melatonin (17, 23-27).

As to the melatonin biosynthesis in vertebrates, tryptophan is the precursor. Throughout the processes of hydroxylation, decarboxylation, acetylation, and methylation in order, tryptophan is converted to melatonin. The acetylation step is catalyzed by the aralkylamine N-acetyltransferase (AANAT) which is the rate-limiting enzyme for melatonin synthesis and its activity is regulated by the light/dark cycle (28). The light intensity detected by the retina is the neuronal signal via the retinohypothalamic tract transmitted to the suprachiasmatic nucleus of the hypothalamus. This leads to the alteration of norepinephrine release into the pineal perivascular space of the pineal gland (28, 29). Norepinephrine then acts on β1-adrenergic receptors leading to activation of downstream signaling via adenylyl cyclase, causing an increase in intracellular calcium (Ca^{2+}) concentration, phosphokinase C activity (30, 31), and a rise in cAMP concentration in the pinealocytes (30, 32–34). cAMP is responsible for modulating AANAT activity by causing an increase in AANAT affinity for arylalkilamines (28, 35–37).

2. MELATONIN AND *PLASMODIUM*

Malaria is a severe disease caused by parasites of the *Plasmodium* genus and was estimated to be responsible for the infection of 229 million people and 409 thousand deaths in 2019 globally (38). Among *Plasmodium* species, *P. falciparum*, *P. ovale*, *P. malariae*, *P. vivax*, and *P. knowlesi* can infect humans (39, 40).

The infection of the host occurs during the feeding process of the female infected mosquito of the *Anopheles* genus, which injects sporozoites into the host bloodstream. The sporozoites migrate and establish the infection in the liver. In the hepatocytes, *Plasmodium* parasites undergo a series of multiplication and develop into merozoites, which are released into the bloodstream. Their intra-erythrocytic cycle starts when merozoites invade the host erythrocytes. During the erythrocytic cycle, *Plasmodium* parasites undergo three well-characterized stages: ring, trophozoite, and schizont, the last one forming merozoites, which are released into the bloodstream from the infected red blood cell (RBC). Merozoites can invade new erythrocytes and continue the asexual intra-erythrocytic cycle. A few parasites are committed to generating the gametocyte forms microgamete and macrogamete; the sexual form of the parasite that infects the mosquito vector. During the feeding process, a female mosquito from the *Anopheles* genus ingests the sexual forms of the parasites, initiating the sexual cycle in the mosquito (41, 42).

The duration of the intra-erythrocytic cycle of *Plasmodium* parasites is generally a multiple of 24 hours, resembling circadian rhythms. Moreover, some *Plasmodium* species development is synchronized with the host rhythms, a process characterized by a release peak of merozoites

in the bloodstream (43, 44). Interestingly, Trager and Jansen (45) observed that *P. falciparum* loses the synchrony when maintained in culture. Among the *Plasmodium* species, only the human parasite *P. falciparum* have a synchronized intraerythrocytic cycle and the rodent parasite *P. chabaudi* (46), whereas *P. yoelli* and *P. berghei* do not exhibit such feature. (47).

Boyd *et al.* (48) investigated the influence of the host circadian rhythm in the chicken parasite *P. cathemerium.* They found that the inversion of female canaries' light/dark cycle is followed by an inversion of the merozoite release peak of the parasite. David *et al.* (49) elegantly showed that it was possible to invert the peak of schizogony of *P. chabaudi* by artificially inverting the host light/dark cycle. The pineal melatonin production is also associated with the light/dark cycle in vertebrates. From this point of view, the relationship between melatonin and *Plasmodium sp.* has drawn great attention of researchers.

To investigate whether melatonin could influence *P. chabaudi* intraerythrocytic cycle, Hotta *et al.* (46) evaluated the effect of pinealectomy on *P. chabaudi*-infected rats. Pinealectomy disrupted the synchrony of *P. chabaudi* and the effect was reverted upon melatonin treatment. The results showed that melatonin triggered an increase in cytosolic Ca^{2+} concentration (46, 50) and pre-treatment with a melatonin-receptor antagonist, luzindole, or with the phospholipase-C (PLC) inhibitor, U73122, prevented these changes. These data indicate that melatonin acts through a receptor and the release of intracellular calcium is mediated by PLC.

Beraldo and Garcia (51) showed that the incubation of parasites with melatonin precursors N-acetylserotonin, serotonin and tryptamine exerts a synchronizing effect and increases the cytosolic concentration of Ca^{2+} in *P. falciparum* in *in vitro* experiments (51, 52). Also, N^1-acetyl-N^2-formyl-5-methoxykynuramine, a melatonin metabolite, causes an increase in cytosolic Ca^{2+} concentration *in vitro* and influences the asexual cycle of *P. falciparum* and *P. chabaudi* (53). On the other hand, *P. yoelii* and *P. berghei*, parasites known for having an asynchronous cycle in the host, are neither influenced by melatonin in terms of synchronization nor change cytosolic Ca^{2+} concentration (47).

To assess the influence of melatonin related compounds on the *P. falciparum* asexual cycle, Schuck and collaborators (54) found that these melatonin-related compounds were able to reduce the increased parasitemia caused by melatonin and three of these compounds to achieve this effect were only required micromolar concentration in *in vitro* condition. Dias *et al.* (55) also treated the parasites with synthetic indole-like compounds, Triptiofen or Melatotosil. The outcome was interesting. Triptiofen was able to stop the parasite cell cycle and did not induce an increase in cytosolic Ca^{2+} concentration while Melatotosil induced an increase in cytosolic Ca^{2+} concentration and increased parasitemia, an effect similar to that when *P. falciparum* was treated with melatonin. These results open the way to explore indole-like compounds as a treatment for malaria caused by parasites that are influenced by melatonin.

Using isolated *P. falciparum* at the trophozoite stage, Beraldo *et al.* (56), observed that melatonin treatment, as expected, increased cytosolic Ca^{2+} concentration. To investigate the source of Ca^{2+}, they incubated the parasites with melatonin in the presence and absence of extracellular calcium. In both situations, the increase in cytosolic Ca^{2+} concentration was similar. This result points out that melatonin triggers a rise in Ca^{2+} concentration by using an internal source.

Alves *et al.* (57) studied whether melatonin treatment could increase cytosolic Ca^{2+} concentration through activation of inositol 1,4,5-trisphosphate (IP_3) receptor in the sarcoplasmic reticulum of *P. falciparum.* They used a labelled PLC-substrate, [3H-*myo*] inositol, and observed that melatonin treatment increased the metabolization of [3H-myo] inositol and increased cytosolic Ca^{2+} concentration. Using caged IP_3, a way to control the intracellular IP_3 concentration, the authors observed an increase in cytosolic Ca^{2+} concentration

after induction of IP_3 release. To elucidate whether melatonin and IP_3 act in the same route to increase cytosolic Ca^{2+} concentration, *P. falciparum* was treated with melatonin followed by induction of cytosolic IP_3 release, and the characteristic IP_3-induced increase in cytosolic Ca^{2+} concentration was not observed. Thus, the downstream signaling of melatonin involves the activation of PLC and IP_3 formation, which acts on the putative IP_3 receptor at the sarcoplasmic reticulum, leading to the release of Ca^{2+} in the cytosol (57–59). Although IP_3-induced Ca^{2+} release was demonstrated to be important, the IP_3 receptor in *Plasmodium* is not yet identified. Using affinity chromatography and bioinformatic analysis, Alves *et al*. (57) identified the multi-drug resistance 1 (MDR1) transporter as a possible IP_3 receptor (60). Still, more research is needed to confirm this hypothesis.

To elucidate whether the protein kinase A (PKA) would be involved in the intracellular signaling activation induced by melatonin in *Plasmodium*, Beraldo *et al*. (56) started an investigation with this kinase. To do so, they tested the influence of the cAMP analog, 6-Bz-cAMP, and the PKA inhibitor, PKI, in asynchronous *P. falciparum* cultures after melatonin treatment. Melatonin treatment caused an increase in parasitemia and also accelerated schizont formation. Treatment with 6-Bz-cAMP had the similar effect as melatonin, which was the increase of the schizont stage, while treatment with PKI prevented it (56). This is strong evidence that melatonin triggers downstream signaling involving cAMP and PKA.

The mitogen-activated protein kinase (MAPK) is a family of proteins that are involved in response to external stimuli in eukaryotic cells and are present in diverse organisms such as plants, mammals, and unicellular organisms (61). The regulation of MAPK activation involves a phosphorylation cascade, starting with the MAPK kinase kinase (MAPKKK) phosphorylating MAPK kinase (MAPKK), which phosphorylates MAPK (62, 63). Using BLAST analysis, Doring *et al*. (64) identified the protein kinase 7 (PfPK7), a MAPKK related protein in the *P. falciparum* genome, and the result was quite interesting: the C terminal is highly similar to MAPKK, and the N terminal to a fungal PKA. Using *P. falciparum* expressing a non-functional PfPK7, the authors (64) also observed that MAPKK and PKA inhibitors showed no effect in this strain, indicating that the classical MAPKKK-MAPKK-MAPK phosphorylation cascade did not occur in *P. falciparum*.

In 2020, Dorin-Semblat *et al*. (65) observed that the *P. falciparum* PK7 knockout ($PfPK7^-$) strain had a lower parasite growth. Moreover, using $PfPK7^-$, Koyama *et al.* (66) identified that this kinase was involved in the downstream signaling activated by melatonin. Treatment of $PfPK7^-$ parasites did not induce the characteristic synchronization exerted by melatonin in the wild-type strain, indicating that this kinase is essential for synchronization caused by melatonin. In addition, Koyama *et al*. (66) evaluated whether melatonin treatment would be able to affect the expression of genes related to the ubiquitin-proteasome system. A 5 hour-melatonin treatment in *P. falciparum* trophozoite stage (wild-type and $PfPK7^-$ strain) upregulated 13 of 14 studied genes in the wild-type strain and, interestingly, this effect was not present in $PfPK7^-$ parasites. Another kinase involved in the downstream response to melatonin in *P. falciparum* is the eukaryotic initiation factor 2 (eIF2) kinase 1 (PfeIK1). Melatonin cannot induce an increase in parasitemia in *P. falciparum* lacking PfeIK1, indicating that this kinase might be important for the synchronization effect exerted by melatonin *in vivo* (55). The eIF2α kinases family is responsible for phosphorylating the α subunit of eIF2, leading to the repression of the general translation of proteins (67).

As PKA is a kinase involved in melatonin downstream signaling in *P. falciparum*, Lima *et al*. (68) observed that treatment with 6-Bnz-cAMP, a PKA activator, caused an increase in levels of the transcription factor PfNF-YB in the trophozoite stage, and that melatonin treatment increases the ubiquitination of this transcription factor. These results indicate that melatonin treatment regulates PfNF-YB levels via ubiquitination through PKA and the second messenger $_c$AMP. The transcription factor NF-YB binds to a CCAAT-box DNA sequence in

the genome and modulates the expression of several genes in mammals (69–71). Although *P. falciparum* also expresses NF-YB (72), it is still unknown which genes are regulated by this particular transcription factor in this parasite.

A recent study has shown the rhythmic expression of genes in *P. falciparum* and *P. chabaudi*, suggesting that the parasites possess an intrinsic clock responsible for their rhythms (43). Considering the results of gene expression regulation induced by melatonin, Lima *et al.* (73) performed RNA-seq analysis of *in vitro P. falciparum* in the trophozoite stage after melatonin treatment and 38 genes were differentially expressed. These genes include the regulator of initiation factor 2 (eIF2), ubiquitin-40S ribosomal protein, protein tyrosine phosphatase PRL, EMP1 traffic protein PTP4, heterochromatin protein 1 (HP1), and DNA repair endonuclease (73). The results suggest that melatonin plays a key role to modulate the cell cycle of *Plasmodium* within the host through gene regulation. Treatment with melatonin modulates the expression of Mitochondrial Fission Protein 1 (*FIS1*) and the GTPases Dynamin 1 (*DYN1*) and Dynamin 2 (*DYN2*) genes, that encode proteins related to mitochondrial fission (74). There is no alteration in the expression of FIS1, DYN1, and DYN2 in the *P. falciparum* PfPK7^{-} strain, indicating that PfPK7 is a kinase involved in modulating mitochondrial-fission gene expression (74). FIS1 is a protein involved in the fragmentation of the mitochondrial network and its action depends on the GTPases DYN1 and DYN2 in *P. falciparum* (74, 74). Corroborating with this idea, PfPK7^{-} parasites have a slower multiplication rate due to the lower production of merozoites (65). Therefore, these data indicate that the mitochondrial fission step is very important to the generation of merozoites, the last intra-erythrocytic stage and that PfPK7 participates in this process. In addition, an increase in the *michorchidia* (MORC) protein levels under melatonin treatment in intra-erythrocytic stages of *P. falciparum* has been observed (76) and this effect is absent also in the PfPK7^{-} strain. MORC is a protein found in plants and animals identified as a gene regulator by mediating chromatin remodeling, gene silencing, and epigenetic regulation (77, 78). *P. falciparum* expresses this protein - PfMORC - in its nucleus, but its function is not yet fully understood (61, 64). This information warrants further studies to identify the function of PfMORC in the *Plasmodium* intra-erythrocytic stages.

Although melatonin can activate several signaling pathways in *Plasmodium*, its receptor in this parasite is yet to be discovered. Melatonin receptors in humans are G protein-coupled receptors (GPCR), known for their serpentine characteristic with seven transmembrane domains (80, 81). Using *in situ* analysis, Madeira *et al.* (82) identified four serpentine receptors candidates in the *P. falciparum* genome, namely: PfSR1, PfSR10, PfSR12, and PfSR25.

In addition to melatonin-mediated activation of internal signaling cascades in *Plasmodium sp*., this molecule can also modulate the course of its infection in the host. By treating *P. yoelii*-infected mice with melatonin, Guha *et al*. (83) demonstrated a significant reduction in liver mitochondrial apoptosis and liver damage. The influence of melatonin in cerebral malaria has also been studied in *P. berghei* infected mice (84). This treatment prevented cerebral edema and impairment of the blood-brain barrier. Oral melatonin (3 mg) was reported to increase *Plasmodium* detection in the peripheral blood of patients (85). This result corroborates well with the result of Beraldo *et al*. (51), i.e., a significant increase in the schizonts forms was found when *P. falciparum* culture was treated with melatonin for 24 hours. The potential mechanisms of host melatonin on the *Plasmodium falciparum* life cycle are illustrated in figure 1.

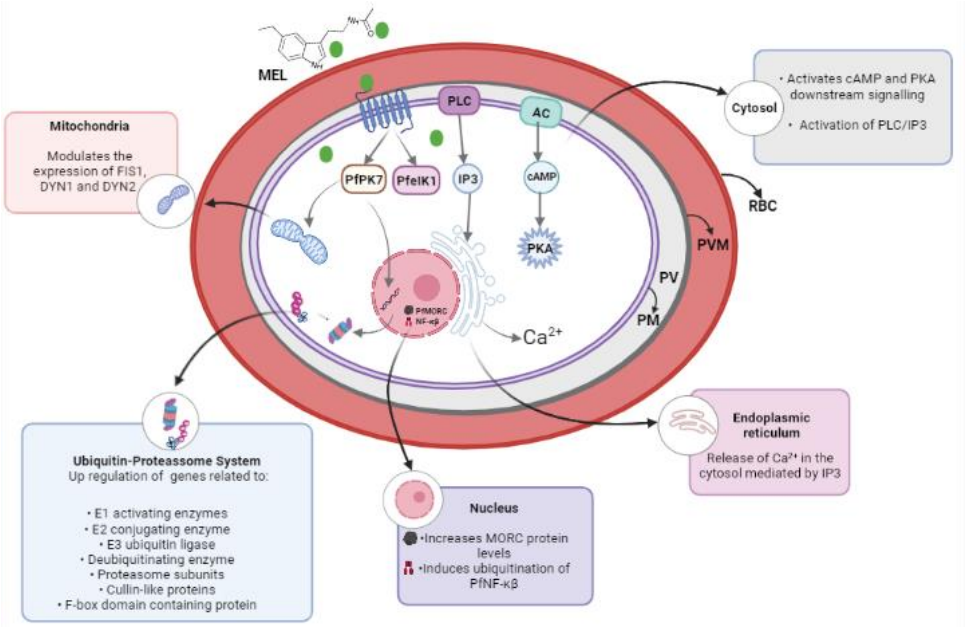

Fig.1: **Schematic representation of the effects of melatonin in *Plasmodium falciparum*.**
Mel – melatonin; RBC – red blood cell; PVM – parasitophorous vacuole membrane; PV – parasitophorous vacuole; PM – parasite membrane; Created in BioRender.com.

3. MELATONIN AND *TRYPANOSOMA CRUZI*

Chagas disease is caused by *Trypanosoma cruzi* (*T. cruzi*) infection, with an estimation of 30,000 cases per year in the Americas and 12,000 deaths per year (86). The parasite cycle depends on the human host and the transmitting vector, which is an insect from the *Triatominae* family. The trypomastigotes of the parasite released during the blood sucking of the vector are transported to the wound or mucosa where they invade into the local cells. Inside the cells, the parasites develop to the stage of amastigotes and trypomastigotes, with the last being released in the bloodstream. From the blood, the trypomastigotes either initiate another cycle of cell invasion or are ingested by the vector (87).

The acute phase of infection is characterized by the presence of parasites in the bloodstream and can be asymptomatic. However, the chronic phase of Chagas disease is characterized by the presence of the parasite in tissues such as the heart and intestine (88). Although the etiology of the complications caused by Chagas disease is not fully understood, evidence shows that the immune system response plays a role in it (89, 90). Therefore, understanding the immune response against T. cruzi infection is essential to modulate the innate immune system against the parasite.

Santello *et al*. (91, 92) observed that melatonin-treatment concomitant with or before *T. cruzi* infection led to a decrease in parasitemia. In addition to acting as a free radical scavenger, melatonin treatment also influences the activity of the immune system with an increase in TNF-α, IFN-γ, IL-12, IL-2, a decrease in IL-4 levels, induction of leukocyte production, and suppression of Th2 response in Chagas disease (91–95). The main hypothesis of the decreased parasitemia levels upon melatonin treatment relies on the immunoregulatory effects of melatonin during the infection (91–95). For example, orchiectomy combined melatonin treatment had a synergistic effect on leukocyte count and IL-2 and IL-12 production (94). Melatonin combined with dehydroepiandrosterone (DHEA) treatment on acute-*T. cruzi* infected rats led to an increase in peritoneal macrophages and TNF-α levels and a decrease in parasitemia (95). The middle-aged rats infected with *T. cruzi* treated with melatonin

caused the reduction of the steroidal hormones of corticosterone, 11-dehydrocorticosterone, cortisol, cortisone, aldosterone, and progesterone levels (96). The results indicate a close relationship between melatonin treatment and hormones in the progression of Chagas disease.

To explore the action of melatonin as a free radical scavenger in *T. cruzi* infection, Brazão *et al.* (97) observed that this indoleamine can decrease the production of superoxide (O^{2-}) in the thymus of infected animals and increase superoxide dismutase (SOD) activity, a natural antioxidant (97, 98). The association of melatonin with zinc, an antioxidant and anti-inflammatory agent, has been studied and its crosstalk neutralizes immune dysregulation induced by the parasites in the chronic stage (99, 100). Melatonin treatment diminished the burden of amastigotes in heart tissue leading to less cardiac damage during the acute phase (92). The beneficial effects of melatonin can also be observed in the chronic phase as melatonin can diminish the inflammatory foci and cardiomyocyte damage in chronically infected mice (101). Despite the positive results in cardiac tissue, a recent study shows no diminishment in parasite replication and an accelerated parasitic release during the acute phase of infection in infected mice treated with melatonin (102). Therefore, more study is necessary to assess the risk-benefit use of melatonin in *T. cruzi* infection.

4. MELATONIN AND *LEISHMANIA*

Considered a neglected tropical disease, Leishmaniasis is caused by protozoan parasites from *Leishmania* (L.) genus (103, 104). Worldwide, Leishmaniasis causes approximately 20,000–30,000 deaths annually, and it is estimated that there are 12 million people infected (105). The parasite is transmitted by phlebotomine sandflies and is an obligatory-intracellular parasite, with part of the cycle in macrophages phagolysosomes (106, 107).

Laranjeira-Silva *et al*. (108) reported that the time of infection could alter the outcome of this infection by *L. amazonensis* in rats. The animals inoculated with the parasite in the dark phase had smaller lesions than the animals inoculated in the light phase. To confirm whether endogenous melatonin could interfere with the infectivity of *L. amazonensis*, a pre-treatment with luzindole (melatonin receptor antagonist) before melatonin treatment was performed, and they observed reduced lesions caused by the parasites. An *in vitro* invasion assay also observed a reduction in *L. amazonensis* infectivity in melatonin-treated-murine macrophages.

Emahallawy (109) observed that melatonin treatment decreases *L. infantum* growth *in vitro*. They also found that melatonin triggered the opening of the permeability transition pore (PTP), a structure present in mitochondria whose opening is related to cell death by compromising the mitochondrial membrane potential. Along with action in PTP, melatonin also impaired mitochondrial complex chains I, II, and III, components of the electron transport chain of *L. infantum* (109, 110). These actions of melatonin might be responsible for the decrease of parasite growth under melatonin treatment.

5. MELATONIN AND OTHER PARASITES

Toxoplasma gondii is the parasite responsible for toxoplasmosis disease. By treating *T. gondii*-infected rats with melatonin, Baltaci *et al*. (111) observed an increased leukocyte count in the bloodstream. In addition, *T. gondii*-infected macrophages treated with melatonin reduced parasite proliferation and apoptosis-induced death (112). In the absence of indoleamine-pyrrole-2,3-dioxygenase-1 (IDO1), the enzyme that catabolizes tryptophan, the *T. gondii* increases the biosynthesis of melatonin, which, interestingly, causes an increase in parasite growth and decreases levels of reactive oxygen species (ROS) (113). Further studies are necessary to better understand the action of internal and external melatonin in *T. gondii*.

Schistosomiasis is a disease caused by the parasite *Schistosoma sp*. The main complication of the disease is the formation of granuloma in the liver, causing liver fibrosis and portal hypertension (114). Knowing that the oxidative process is essential for the progression of schistosomiasis (114–117), El-Sokkari *et al.* (117) treated *S. mansoni*-infected rats with melatonin. The first parameter analyzed was the death rate of the infected mice, with a substantial reduction in the melatonin group. A decrease in granuloma formation was observed at the tissue level and diminished or prevented pathological changes caused by *S. mansoni* in the kidney, liver, and spleen. Melatonin reduced NO, inducible nitric oxide synthetase, and lipoperoxidation levels in *S. mansoni*-infected mice (117). The elevated level of ROS, including nitric oxide (NO), reflect the increased oxidation and tissue damage (118).

Opisthorchis viverrini is an inductive-cholangiocarcinoma parasite that is endemic in Southeast Asia (119, 120). Laothong *et al*. (121) observed that hamsters infected with *O. viverrini* treated with melatonin decreased liver injury, DNA damage, and increased nuclear factor-erythroid 2-related factor-2 (Nrf2) expression. Nrf2 is a transcription factor responsible for regulating response against oxidative damage (121). Also, melatonin caused the downregulation of oxidant genes, such as NF-κB, iNOS, COX-2, and reduction of proinflammatory cytokine expression in parasitized animals (122).

The amoebiasis is due to the *Entamoeba histolytica* parasite. The infection leads to an inflammatory process with immune cell recruitment, triggering tissue damage (123). França-Botelho *et al*. (124) treated *E. histolytica*-infected hamsters with melatonin and observed decreased hepatic necrosis and inflammatory infiltrate while the increased activity of leukophagocytosis. These results indicate immunomodulatory effects of melatonin against infection caused by *E. histolytica*.

6. CONCLUSION

Melatonin, a host hormone, is capable of modulating parasitic infection by preventing tissue damage, regulating gene expression and inflammatory process, and acting as a free radical scavenger. So far, the influence of melatonin-related compounds as precursors, metabolites, and indolic molecules was studied in *Plasmodium sp*. parasites with interesting results, such as an increase in parasitemia and activation of intracellular signaling cascade. Therefore, further study of the net of intracellular players involved in this cascade is essential to bring light to the host-parasite relationship and is a promising path for further studies with other parasites. An understanding of the influence of melatonin and melatonin-related compounds in parasitic infections can help cast more light on host-parasite interactions and find a way to block parasite multiplication within the host.

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AUTHORSHIP

CRGS and JMP contributed to the critical review and approval of the text. RIH contributed to reading the literature, preparing the manuscript and figures. BKMD contributed by structuring the manuscript and revising it along with the figure.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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