Review

Melatonin: A review of its physiopathological and therapeutic relationship with parasitic diseases

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ABSTRACT

Melatonin (MEL), an indoleamine hormone synthesized in almost all organisms including humans, has been the object of a considerable body of research due to its pleiotropic functions. Recently, focus has been given to its roles as a regulator of the immune and inflammatory response, in the context of numerous disorders; likewise, it has been studied as a potential therapeutic option in numerous infectious diseases. In this sense, the relationship between this molecule and parasitic infections is of particular interest; thus, the present review aims to compile knowledge acquired in the last few years, regarding the participation of MEL in the pathophysiology of parasitic infections, and its potential clinical applications. Since parasitic diseases still represent a significant burden on health systems worldwide, particularly in low and lower-middle income countries with limited access to sanitation facilities and resources for therapeutic approaches, the continuing study of MEL, as an affordable and fundamentally safe healing option, might help better control of these infections.

Key words: melatonin, parasites, *Plasmodium, Toxoplasma, Trypanosoma, Leishmania*

1. INTRODUCTION

Melatonin (MEL) is an indoleamine hormone, primarily produced by the pineal gland following a circadian rhythm with its peak level at night and baseline during the day, first described by Lerner *et al*. in 1958 (1); thereafter, the molecule has been found in different species, even in unicellular organisms, a fact which supports its phylogenetic antiquity (2). In addition to pineal gland, synthesis of MEL has been identified in several other tissues and organs, including the retina, gastrointestinal tract, immune system, airway epithelium, and kidney (3). In humans, the indoleamine is involved in numerous biophysiological processes, including regulation of circadian rhythms and sleep (4-7), immunomodulation (8-10), defense against viral infections (11-14), bone formation (15), and tumor suppression (16-18).

Melatonin has important antioxidant and neuroprotective activities (19-24). Administration of MEL has been proposed as an option for the treatment of disorders such as sleep disturbances, depression, cancer, cerebrovascular, and neurodegenerative diseases and epilepsy, although a clinically effective regimen has yet to be established (17, 25-29, 30). One of the most important findings regarding the properties of this hormone is its intricate immunomodulatory function; it activates both the cellular and cytokine response (31), and

stimulates the immune response under basal or immunosuppressive conditions while it inhibits the immune response during acute/chronic inflammation (32). This differentiated immunoregulatory profile, seemingly dependends on the conditions of the milieu, and its potential impact in aging, neurodegenerative, autoimmune and mood disorders, has been the object of extensive research (33, 34).

Studies in the last decade have helped to better understand the mechanisms of action of the molecule. Although MEL freely diffuses through all biological membranes, its activity can also be receptor mediated. Cell surface membrane receptors of MEL include MT_1 and MT_2, G-protein coupled receptors; the MT_1 receptor has additionally been reported in the outer mitochondrial membrane, with MEL from the mitochondrial matrix diffusing out of the organelle and binding to the receptor on the outer membrane, in a process described as "automitocrine", possibly related with the response to oxidative stress and the modulation of apoptosis (35). There are binding sites in the cytosol and in the nucleus; in the cytosol, quinone reductase 2 (QR2), a detoxifying enzyme, has been designated as MT_3, its activity likely associated with reduction in oxidative damage. In the cytosol, the indole can bind to calmodulin, a phenomenon conceivably linked to cancer inhibition (36). Multiple MEL receptor isoforms have been related to differential tissue regulation throughout the lifespan of organisms, and selective pathways for intracellular signal transduction have been proposed (37-39). The variety in the signaling pathways and biological processes in which the hormone is involved might explain the array of potential applications.

One of the instances that best illustrates the interconnection between the different biological properties of the indole involves studies of the administration of MEL in viral infections. In mice infected with the Venezuelan equine encephalitis (VEE) virus, MEL reduces the death rate and evolution of the disease (11); and, in mice immunized with an attenuated strain of the VEE virus, administration of MEL, starting before and after immunization with the virus, increases blood IgM titers, coinciding with rises in IL-10 levels (40). In this same line of research, in brain homogenates from mice inoculated with the VEE virus, with/out 500 mg MEL/kg body weight, levels of TNF-α and IL-1β were measured; in MEL-treated mice, injected daily starting 3 days before and continuing to 7 days after virus inoculation levels of TNF-α were decreased on days 1, 3, 4, and 5 post-inoculation compared to the control ($P < 0.001$); conversely, IL-1β levels were increased from days 1 to 5 compared to controls ($P < 0.01$) (41). In VEE virus infected mice, exposed to high intensity light (2500 lux) during the light phase of a light/dark cycle (12/12h), an increase in both concentrations of MEL and survival rate has been observed , from 6 to 13 days subsequent to inoculation of the virus (42); the elevation of MEL was observed in the olfactory bulb of mice infected with the virus, and such increase, in the context of the high intensity light in virus-inoculated mice, could be responsible for the increment in survival (43). Even in immunodepressed conditions, MEL could help boost the immune response; in effect, in animals treated with dexamethasone, to suppress the immune response, and inoculated with the VEE virus, MEL increased levels of GM-CSF, at least on the first day of treatment, although concentrations decreased afterwards (44). During infection with the VEE virus, mice splenocytes generate significant amounts of nitric oxide (NO); treatment with MEL decreases levels of NO, in agreement with the properties of the hormone as free radical scavenger (45). Studies with luzindole (LZ), a competitive MEL receptor antagonist which does not inhibit the antioxidant properties of the hormone, have shown that the protective effect of MEL is mediated by its receptors in the immune cells: Valero *et al*. examined the effect of LZ in mice treated with MEL daily 3 days before and 5 days after infection with the VEE virus; in mice infected with the virus and treated with MEL and LZ, mortality was increased compared with animals which only received MEL (46). Besides the extensive study of the effects of MEL on VEE virus infection, the potential therapeutic benefits of the indole have been analyzed in clinical studies of SARS-CoV-2

infection (47), and the neurohormone has been shown to exert a plethora of protective actions, in an *in vitro* model of Zika virus infection (48), and in animal models of several other viral infections, including the rabbit hemorrhagic disease virus, murine leukemia virus, encephalomyocarditis virus, Semliki Forest virus, Aleutian mink disease virus, and an attenuated strain of the West Nile virus (49).

These and related findings generally support the use of MEL in the treatment of infectious diseases; in recent years, different research groups have examined the effects and participation of the molecule in the setting of parasitic diseases. Parasitic infections are a global public health problem, especially in developing countries, by their high prevalence rates, morbidity, mortality, and resistance to treatment (50-53). Recent efforts have expanded the knowledge on the influence of host-synthesized MEL on the cycles of different parasite species (54); likewise, in various disorders of parasitic etiology, the participation of MEL has been described, and its effect on mitochondria, in addition to its immunomodulatory, antioxidant, anti-inflammatory, and neuroprotective effects, support its potential additional therapeutic alternative or as a complement to fight parasitic infections (55). As a continuation to a review on the properties of the indoleamine and its participation in different disorders (56), here we present recent insights on the potential pathophysiological and clinical relevance of the hormone in several parasitic infections.

2. *PLASMODIUM* BIOLOGY, DIAGNOSIS AND TREATMENT: EFFECTS OF MELATONIN

Malaria, caused by species of the genus *Plasmodium*, is the most important parasitic infection worldwide, causing annually high rates of morbidity and mortality. In 2020, 241 million cases of malaria were estimated, in 85 countries where the disease is endemic; most of the cases reported in the African Region (57). Although advances have been made in the control of the transmitting vector, many challenges remain to be solved (58). Recently, several avenues for research have emerged concerning the participation of MEL in distinct facets of the physiology of the species *P. falciparum* and *P. chabaudi*, with potential therapeutic implications.

2.1. Melatonin in the synchronous maturation of *Plasmodium falciparum* and *Plasmodium chabaudi.*

The synchronous maturation of *P. falciparum* and *P. chabaudi*, essential for their life cycle, interaction with host cells, and immunopathology, seems to be linked with the circadian changes in the concentration of MEL; findings in this area indicate that the homeostasis of cAMP, Ca^{2+} and inositol-3-phosphate (IP3) are key components in the connection between the parasite and MEL. It has been postulated that, in *P. falciparum*, MEL crosses the erythrocytic membrane and reaches a receptor located in the parasite plasma membrane. Thereafter, MEL signaling activates phospholipase C (PLC), inducing the production of IP3 which mobilizes intracellular Ca^{2+} from the endoplasmic reticulum, leading to a rise in cytosolic Ca^{2+} concentration (59). In *P. chabaudi*, MEL also stimulates the enzyme adenylyl cyclase, increasing cAMP levels and activating proteinkinase A (PKA), involved in gene expression control in the parasite nucleus, and, potentially, in the regulation and synchronization of the parasite cell cycle (60, 61).

Either pinealectomy or the administration of LZ desynchronizes the cell cycle of *P. falciparum* and reduces parasitemia (62). Beraldo *et al*. showed that, in *P. falciparum*, MEL increased cAMP levels in 40% and the activity of PKA in 50%, as compared to untreated cells; increases in MEL-induced cAMP were inhibited by the PLC inhibitor, U73122 (63). It has also

been reported that both MEL and its precursor N-acetyl-serotonin (NAS) may pass through the *P. chabaudi* membrane, stimulating the generation of IP3 and mobilizing intracellular Ca^{2+}; LZ and U73122, a PLC inhibitor, inhibited this event (64). In the same regard, evaluation of development and morphology have indicated that LZ causes profound alterations to the intraerythrocytic maturation of *P. falciparum*, leading to parasitic death; the administration of LZ, during the ring phase, arrests progression into subsequent phases, while the substance added during the trophozoite phase prevents development into late schizonts. Based on imaging studies, treatment with LZ abolishes Ca^{2+} oscillation in the ring forms, with little effect on early trophozoites, and increase in cAMP after treatment with MEL, at the ring and late trophozoite phases, is attenuated with LZ (65).

The findings by Pecenin *et al*. supported the relevance of IP3-induced Ca^{2+} release in the intraerythrocytic cycle of *P. falciparum*; the authors evaluated the effect of two derivatives of 2-aminoethyl diphenylborinate (2-APB), an IP3 receptor antagonist and inhibitor of store-operated Ca^{2+} entry, (SOCE), DPB162-AE and DPB163-AE, which blocked the MEL-induced rise in parasite cytosolic Ca^{2+} and SOCE at high concentrations, while also affecting the intraerythrocytic development and the ability to invade new red cells; further antagonism of IP3 proved to be lethal to the parasite during the intraerythrocytic cycle (66).

Dias *et al*. comparing the 3D7 strain of *P. falciparum* (wild-type), with a knockout strain for the eukaryotic initiation factor 2-alpha kinase 1 (PfelK1-) and studying the impact of new MEL-derived substances on *P. falciparum* cycles, reported that PfeIK1 plays a vital role in the synchronization of the erythrocytic cycle in *P. falciparum* dependent on MEL, since parasites lacking this kinase presented no significant difference in parasitemia after treatment with the hormone. The group also found a similar reaction between the knockout and the wild-type under oxidative and mitochondrial stress associated with the administration of the classical antimalarials, atovaquone and artemisinin, indicating that the lack of PfeIK1 did not affect the susceptibility of the parasite to these drugs. Likewise, novel indole compounds were evaluated; melatotosil was identified as a potential MEL receptor partial agonist, increasing parasitemia while inhibiting the action of MEL, in 3D7; on the other hand, triptosil showed no effect in 3D7 parasitemia, while potentially abolishing the effect of MEL. The treatment of PfeIK1- parasites with the synthetic indoles and MEL had no impact on parasitemia compared to controls. The authors concluded that PfeIK1 plays a role in parasite synchronization, and the synchronicity by MEL, concurrently suggesting that the MEL pathways involved in synchronization and cell cycle progression could be divergent (67).

2.2. Melatonin synthesis and melatonin pathways: inhibition for the treatment of malaria.

Inhibition of either MEL synthesis or MEL pathways as a therapeutic approach in malaria has been evaluated by several groups. Bright light during nocturnal hours, to suppress plasma MEL synthesis, and the use of anti-kinase drugs, have been suggested as adjuvant treatments (68, 69). Likewise, research has been made on the use of different indole compounds, whether synthetic or naturally occurring, capable of inhibiting the MEL pathways and interfering with the maturation of the parasite. Shuck *et al*. studied the effect of ten indole compounds on the synchronization of the *P. falciparum* erythrocytic cycle triggered by the hormone and parasite growth; eight compounds impaired the effect of MEL on synchronicity at a concentration of 500 nM, combined with 100 nM of MEL. Furthermore, three compounds possessed activity against *P. falciparum in vitro*; modification of the carboxamide group attached at the C-3 position of the MEL indole ring was crucial for the action of the compounds (70). Luthra *et al*. reported a novel class of antimalarials based on C2-arylalkanimino tryptamine derivatives, tested against an asynchronous culture of parasites. Preliminary screening against the 3D7 strain revealed that one compound, 2b, inhibited parasite proliferation by 47%; in comparison,

inhibition with LZ, the positive control, reached approximately 48%. A library based on 2b was then designed; intraerythrocytic parasite cycle progression, particularly during the trophozoite stage, was inhibited by the most active compounds from the series (compounds 2g, i, j, k and p), and interrupted the MEL-induced synchronization of parasite growth. Compounds 2g, i, j, k and p were also effective against the chloroquine-resistant RKL9 strain. According to the authors, the effect of the compounds could be explained by MT_1 inhibition (71). Similarly, Lunga *et al*. studied the structure and function of several indole compounds with C5, C2, and C3 substituents; methylation at C2 decreased the activity of the compounds, while the addition of a chloride radical in C5 was associated with the best result (72). Dangi *et al*. tested different indole compounds, derived from usambarine and aspidocarpine, and identified two substances able to significantly inhibit parasite growth, with one of the derivatives affecting the balance of Na^+ and arresting the parasite cycle during the trophozoite stage (73). Relatedly, Mallaupoma *et al*. evaluated the properties of synthetic indole compounds (14 in total), when administered to the 3D7 and Dd2 strains of *P. falciparum*, respectively chloroquine-sensitive and chloroquine-resistant. Compounds 3, 26, 18 and 21 reduced 3D7 growth (50%), and a group of 2- sulfenylindoles displayed an anti Dd2 action profile. The impact of the 14 compounds on 3D7 parasitemia, as well as the possible influence on the effect of MEL on parasitemia of this strain was likewise evaluated; the investigators indicated that some of the compounds (specifically, compounds 3, 7, 8, 10, 14, 16, 17, and 20) contributed to the MEL-mediated elevation in parasitemia (8–20%) versus exclusive treatment with MEL. Thus, the authors emphasized these data as support for the potential antimalarial efficacy of sulfenylindoles, in cases of resistance and susceptibility to chloroquine, even if certain compounds could elevate parasitemia (74).

Finally, two enzymes essential for protein translation, tryptophanyl-tRNA synthetases, were identified in *P. falciparum*: one located in the apicoplast (TrpRSApi) and one in the cytoplasm (TrpRSCyt); authors tested, *in vitro,* a natural tryptophan analogue, indolmycin, and two indolmycin analogues, against *P. falciparum*; it was reported that *P. falciparum* growth was inhibited and its delayed death elicited by the effect of indolmycin, which interferes with the function of the apicoplast, targeting TrpRSApi (75).

2.3. Effect of melatonin on *Plasmodium* gene expression.

The effect of MEL on the expression of different genes has shed more light on the involvement of the hormone in the parasite biology. It has been reported that the MEL-induced maturation of *P. falciparum* is accompanied by increased expression of the FIS1 and DYN1 genes, involved in mitochondria fission and several cytoplasmic processes (76). Lima *et al*. evaluated the expression profile of MEL- and cAMP-regulated *P. falciparum* genes, via RNA-sequencing (RNA-Seq) analysis in three strains (control, 3D7; protein kinase 7 knockout, PfPK7- ; and PfPK7 complement, PfPK7C). After treatment with MEL, the differential expression in 38 genes of the 3D7 strain was reported; the indoleamine affected mRNA expression of genes which encoded proteins in the plasma membrane, zinc ion-binding proteins and proteins which bind to nucleic acids, actors in different functions. On the other hand, the hormone did not modify the gene expression in the trophozoite stage PfPK7- knockout parasites, when compared to untreated controls, hinting that PfPK7 might participate in MEL signaling and the related changes in gene expression. The RNA-Seq data after treatment with cAMP indicated a differential gene modulation along the intraerythrocytic cycle. On the basis of these findings, authors highlighted the environment-perception capability of the parasite, via MEL and cAMP signaling, which in turn can modify parasite gene expression, including PfNF-YB, a parasitic nuclear transcription factor that plays an important role in cell division during intraerythrocytic stages (77, 78).

Koyama *et al*. reported that the expression of ubiquitin/proteasome system (UPS) genes in *P. falciparum*, in which PK7 also participates, can be affected by treatment with MEL or NAS. Based on real-time PCR analysis of MEL and NAS treated samples, the researchers identified 6 genes consistently regulated by both substances: ubiquitin C-terminal hydrolase, ubiquitin activating enzyme E1, hypothetical protein containing the F-box domain, culin-like and proteasome subunit, this last one a nonenzymatic component essential for ubiquitinated protein degradation, and for both *Plasmodium* and *Trypanosoma* survival. Thus, MEL would appear to control both general protein ubiquitination via modulation of E1 and the proteasomal subunit, or more specific genes like deubiquitinases and E3 ligase. A chronological variation in gene expression led researchers to propose the existence of a cascade of UPS gene regulation and protein ubiquitination, with parasite proteins being differentially ubiquitinated over time, when exposed to MEL, resulting in a delicate control of gene transcription, dependent on temporal requirements (79, 80).

Singh *et al*. evaluated the effect of MEL on the expression of PfMORC, a nuclear protein with a histidine kinase domain involved in the control of the *P. falciparum* cell cycle. Treatment with MEL affected the expression of the PfMORC transcript in PfPK7 knockout parasites; complementing PfPK7 partially recovered the loss. A time-dependent MEL treatment in wild type *P. falciparum* led to a periodic PfMORC expression pattern, with a constitutively higher expression after 18 h of treatment, suggesting a peak effect of the host hormone during the later stages of parasite development, as well as a participation of the protein in parasite maturation; PfMORC knockdown with glucosamine altered the MEL-dependent parasite synchrony. The authors emphasized the identification of PfMORC as an important *P. falciparum* protein mediating downstream MEL signaling, and further proposed the PfMORC and APETALA2 transcription factor (AP2-TF) interaction, as a conceivable mechanism regulating the asexual cell cycle (81).

2.4. Finding a balance: Complexities of melatonin action in malaria.

A dilemma emerges when considering the potential therapeutic applications of MEL in the context of malaria: MEL antagonists, used correctly, could help block parasite maturation; however, the hormone has also been shown to exert protective actions on the host. Indeed, it has been reported that administration of MEL, in elevated doses, exerts an anti-apoptotic effect on mice hepatocytes, in malaria (82), and, in an animal model of cerebral malaria induced by *P. berghei*, a neuroprotective role of MEL against breakdown of the blood-brain barrier, and behavioral impairment evoked by the parasite was reported (83). Such findings highlight the intricacy in the properties of the indoleamine; a well-designed treatment regime, which combines MEL antagonists to interfere with parasite maturation and effective doses of MEL to prevent or minimize tissue damage during the infection, has been advanced (84). Finally, MEL might also be used as a diagnostic tool, since oral administration of the indole could help increase the diagnosis of malaria; indeed, in a prospective study in 80 patients suspected of suffering from malaria, administration of oral MEL was associated with an increase in *P. vivax* and *P. falciparum* detection in peripheral blood smear examination, when compared with controls (85).

3. *TRYPANOSOMA CRUZI*: ROLE OF MELATONIN

In approximately 30% of individuals, *T. cruzi* infection evolves into chronic Chagas disease, representing a public health of grave repercussions in Latin America; the parasitic cell cycle involves the transformation of the epimastigotes towards metacyclic forms, principally under darkness, within the vector gut. These forms are excreted and can infect humans. A link seems

to exist between light, MEL synthesis, and the ability of the parasite to infect humans. In effect, reports have indicated that, cultured in the presence of uninterrupted darkness, epimastigotes synthesize the indoleamine through a 24 h cycle, biphasically, with a high efflux of MEL produced by the parasite into the culture medium, during peaks of its synthesis. Epimastigotes, cultured with 2 h light pulses, have shown a significant reduction in the content of the indole; and, although administration of exogenous MEL had no effect on parasite growth, it decreased its transformation into the metacyclic forms, usually the more synthetically active forms (86).

In a study by Santello *et al*., in rats infected with the parasite and treated with oral MEL (5 mg/kg/bw/day), a significant reduction in the number of blood trypomastigotes during the acute phase of the infection was reported, along with, a decrease in the number and size of amastigote, diminished cardiac inflammation and tissue disorganization, indicative of lessened parasitism. Taken together, MEL might be able to modulate parasite replication, representing an effective therapeutic option for trypanosomiasis (87).

To analyze the impact of the exogenous indole on the immune response to the parasite, MEL was administered to male Wistar rats infected with *T. cruzi*; treatment was supplied in one of two regimens, starting either 7 days before the infection or simultaneous to the infection. The two regimens augmented the levels of TNF-α, IFN-γ, and IL-12, but the administration of the indole simultaneous with the infection was more effective in prompting the response (88). When Wistar rats infected with the Y strain of *T. cruzi* were orally treated with MEL (10 mg/kg/bw/day), and/or received subcutaneous dehydroepiandrosterone (DHEA, which has been demonstrated to exert protective effects against bacterial and parasitic infections), blood trypomastigotes decreased significantly in the acute phase of the infection. During maximum parasitemia, the number of macrophages incremented significantly with the indoleamine; thus MEL, DHEA, or both reduce parasitemia during the acute infection (89). Similarly, in Wistar rats infected with the Y strain of *T. cruzi*, treated with the combination of MEL and the preferential cyclooxygenase-2 inhibitor meloxicam, an increase in serum IL-2 and IFN-γ was observed and augmented NO production by macrophages, with a reduction in parasitemia (90). Other components of the acute response to the infection have been studied. It is believed that oxidative stress and thymic atrophy represent substantive pathophysiologic phenomena of the acute Chagas disease; Brazao *et al*. hypothesized that exogenous MEL, administered by gavage (5 mg/kg) to young (5 weeks old) and middle-aged (18 months old) male Wistar rats, would limit thymic oxidative damage and counter regression of the thymus in the acute disease. Increased levels of superoxide anion were detected in the thymus of infected animals, an increase reverted with MEL; the group found a reduction in 2-thiobarbituric acid reactive substances (TBARS) levels, as well as a significant increase in superoxide dismutase (SOD) activity in the thymus of all middle-aged MEL-treated animals, with or without infection; MEL increased thymic expression of SOD1 and SOD2 in middle-aged controls. Taken together, MEL reverted the age-related thymic regression (based on anatomical and histological indicators), suggesting the new antioxidant features for MEL, potentially useful in the treatment of Chagas disease (91).

Complementarily, the efficacy of MEL as a therapeutic option for chronic Chagas disease has been evaluated, in the context of the immune response to the chronic infection, and in mitochondria- and myocardiocyte-related phenomena. Brazao *et al*. reported that neither zinc nor MEL affected the percentage of CD4+ and CD8+ T lymphocytes, but the levels of IL-2 and IL-10 were increased and thymocyte proliferation was enhanced, and the number of macrophages reduced, in rats chronically infected with *T. cruzi*; thus, zinc and MEL, acting in tandem, might prevent the immune dysregulation induced by the parasite (92). It has also been found that combining zinc and MEL diminishes the ratio of splenic apoptotic cells in infected and treated animals, versus untreated controls; authors suggested that immunomodulation by zinc and MEL could affect the T cell immune response balance, cell survival and the expression

of co-stimulatory molecules during chronic *T. cruzi* infection, modifying the host's immune response against the parasite (93). Moreover, the persistent oxidative stress and the myocardial damage during the chronic progression of Chagas disease could be reduced by MEL; the administration of MT_1/MT_2 agonists, such as ramelteon, which do not affect NO production during the acute phase, and MEL in sufficiently high doses to serve as antioxidant and protect mitochondria, preventing heart damage during the chronic phase, could represent an efficient adjuvant therapy in Chagas disease (94); in this sense, it has been observed that MEL prevents *in situ* mitochondrial potential alterations in muscle cells, and the associated changes in contractility and metabolism (95). MEL therapy has also been shown to protect Wistar rats against the inflammatory response observed in the cardiac tissue, in chronic *T. cruzi* infection: in rats infected with trypomastigotes of the Y strain of *T. cruzi*, initially untreated for 60 days and subsequently treated with MEL (50 mg/kg/day, orally), increased levels of IL-10 and reduced concentrations of NO and TNF-α produced by the cardiomyocytes were found. In these animals, MEL also diminished heart weight, serum creatine phosphokinase-MB (CK-MB) levels, and points of inflammation (96).

Despite these promising results, the beneficial effects of the indoleamine have not been universally observed. Providello *et al.* investigated the effects of MEL on heart parasitism in mice infected with *T. cruzi*, as well as its effects on parasitic proliferation *in vitro.* Even though there was a reduction in the circulating parasite load *in vivo*, MEL was unable to control heart, liver, or spleen parasitism; neither did the hormone prevent the left ventricular redox imbalance of infected mice, and the *in vitro* analysis demonstrated that intracellular parasite replication was not inhibited; on the contrary, parasite release was increased. Taking their results into consideration, the authors emphasized that, albeit the potential of MEL in controlling the circulating parasitic load, due to its immunomodulatory and antioxidant properties, the accelerated tissue proliferation of *T. cruzi* induced by the hormone may hinder its beneficial systemic effects (97).

4. *TOXOPLASMA GONDII* AND MELATONIN: PARASITE BIOLOGY AND TREATMENT

Toxoplasmosis is spread worldwide and infects several mammals, including humans. Evidence of exposure to *T. gondii* has been reported in approximately 30% of people worldwide, with significant regional variability (98). Infection mainly occurs through the consumption of raw or undercooked meat that contains cysts of the coccidium or by ingestion of food, water or soil contaminated with oocysts spread by cats (99, 100). As is the case with other species, the relationship between *Toxoplasma* and MEL has been evaluated, in different contexts**.** Baltaci *et al*. (101) reported that MEL (3 mg/kg) and/or zinc sulfate supplementation (3 mg/kg) daily for 3 weeks may activate cellular immunity by stimulating CD4+ and CD8+ production in rats infected with *T. gondii*; in the presence of MEL deficiency due to pinealectomy, NO levels increase (102); deficiency of zinc and/or MEL negatively influences the cellular immunity in rats with toxoplasmosis (103). Thus, it has been proposed that MEL and zinc could be added to the standard treatment of the infection, especially for *Toxoplasma* retinochoroiditis (104).

Machado *et al*. analyzed the effects of MEL in the epithelial cell line LLC-MK2, after *T. gondii* infection; the group found that the indoleamine had no effect on host cell viability and reduced parasite proliferation in the cells at 24 and 48 h, and at 6 days. A reduction in *T. gondii* reproduction, as well as anomalies in the shape of tachyzoites, was reported via electron microscopy scanning; concomitantly, rupture of the parasite plasma membrane, accompanied by cytoplasmic leakage, was observed with transmission electron microscopy; there was positive staining for parasitic apoptotic-like cell death, after treatment. The authors concluded

that MEL might induce parasite cell death through both necrosis and apoptosis, due to changes in energy metabolism. Thus, the hormone could permanently inhibit *T. gondii* growth at 48 h post-treatment; even after 6 days, no tissue cysts were observed. Based on their results, the authors proposed the indole as a model for the treatment of toxoplasmosis (105). On the other hand, the effect of MEL on NO levels must be considered, when using MEL in the therapy of disease: in effect, the hormone can reduce the activity of induced NO synthase, decrease NO production and diminish the likelihood of neurotoxicity and central nervous system damage, in rodent models of encephalitis by toxoplasmosis (106); but a minimal amount of NO must still be present for proper immunoprotection and immunomodulation.

A fundamental element of *T. gondii* infection in humans is related to the serious consequences of acute toxoplasmosis during pregnancy, with an increased risk of abortion. In a case-control study in Baghdad, Iraq, Al-Kuraishi *et al*. evaluated serum levels of MEL and inflammatory biomarkers in acute toxoplasmosis in pregnant women with recurrent abortions; 60 pregnant women in the first trimester with acute disease (n=28) or without infection (n=32), with a history of recurrent abortions, were compared to a control group of healthy pregnant women (n=25). Concentrations of MEL, IL-10 and IL-12 serum levels were measured. Healthy pregnant women had higher serum MEL concentrations (117.48±34.88 pg/ml) compared to participants with or without acute toxoplasmosis and a history of recurrent abortions; serum IL-10 was significantly higher ($p<0.0001$) in the healthy controls (12.73±2.58 pg/ml) when compared with pregnant women with (5.50±1.92pg/ml) or without acute toxoplasmosis (8.50±2.53 pg/ml). Serum MEL was positively correlated with serum IL-10 levels ($P<0.001$, $r=0.94$), and negatively associated with serum IL-12 in pregnant women with recurrent abortions with or without acute infection. Although the sample was small, and additional important inflammatory markers were not included, the authors emphasized the possible association between recurrent abortions and low MEL serum levels and proposed that administration of MEL could prevent the risk of recurrent abortions in pregnant women with acute toxoplasmosis (107).

Even though recent findings support the use of MEL as part of the treatment against *T. gondii* infections, some groups have reported that the hormone could facilitate certain physiological processes in the parasite. Majumdar *et al*., in a study on a human epithelial cell line infected with *T. gondii*, proposed that the protozoan selectively utilizes tryptophan to synthesize MEL, which stimulates survival of infected cells through the activity of AKT (serine/threonine kinase, involved in the signaling cascade of various cellular stimuli) and β-catenin (a structural protein which participates in several developmental and homeostatic events), enhancing parasitic replication. The authors demonstrated that degradation of tryptophan into kynurenine, accompanied by IFN-γ, abolished phospho-AKT and phospho-β-catenin levels, stimulating cell death; similarly, the administration of kynurenine or its analogue, teriflunomide, into infected cells suppressed the activity of AKT and inhibited the phosphorylation of β-catenin, thus triggering the apoptosis of infected cells, arresting parasite growth. Additionally, it was reported that levels of H_2O_2, produced in the host cells after administration of tert-butyl hydroperoxide, were reduced in infected cells, and this reduction was more pronounced in MEL-treated cells, with a concomitantly augmented parasite growth (108). Undoubtedly, metabolism of the hormone in *T. gondii* and in host cells requires further research.

5. *LEISHMANIA*: PARTICIPATION OF MELATONIN IN PARASITE BIOLOGY AND TREATMENT

The protozoan *Leishmania donovani* causes visceral leishmaniasis (VL), a disease which manifests with irregular bouts of fever, splenomegaly, hepatomegaly, anaemia and weight loss;

tens of thousands of new cases occur annually, throughout the world (109). Different aspects of the relationship between leishmaniasis and MEL have been studied: the potential role of the indoleamine as a therapeutic option, its effect on distinct immune elements, and its participation on the parasite physiology.

In a study by Laranjeira-Silva *et al*., hamsters raised under a long-day photoperiod, during the light phase or the dark phase (at the time of maximum serum MEL), were infected with *L. amazonensis*; the analysis of footpad lesions revealed that a time-dependent progressive pathology took place: animals inoculated with the parasite during the dark phase presented significantly smaller lesions beginning at 14 days after inoculation. Five days after infection, parasite load had been substantially reduced in hamsters inoculated in the dark phase (80%), when compared with hamsters inoculated during the light phase. Thus, inoculation in the dark phase led to decreased parasite replication and lesion evolution, stressing the possible influence of the circadian rhythm on the disease. The authors then hypothesized that MEL could attenuate the infection after inoculation during the dark phase. When hamsters previously treated with 5 mg/kg LZ were infected with *Leishmania* during the dark phase, the lesions in these animals resembled those in animals infected during the light phase and were larger than the ones in controls. However, animals pretreated with 30 ng/kg MEL, infected 1 hr later during the light phase, presented significantly smaller lesions compared with animals infected during the same phase treated with vehicle. Remarkably, at 43 days post-infection, the lesions in MEL treated animals, infected during the light phase, were even smaller than those in animals infected during the dark phase; treatment with LZ reversed the attenuation during the dark phase, and treatment with MEL in animals inoculated during the light phase led to attenuated infection. Thus, the researchers suggested that the attenuation of the infection, in animals infected during the dark phase, was mediated by MEL receptors (110). Likewise, Parvez *et al*. have reported on the administration of a complex involving MEL and amphotericin B (HPCD-Mel-AmB SLN) in a mice model for the treatment of VL. At an orally administered dosage of 10 mg/kg, for 5 days, the combination of drugs significantly reduced the intracellular load of the parasite in liver samples of mice infected with *L. donovani*, leading the researchers to assert the potential of the complex for the treatment of VL (111).

The effect of MEL on certain elements of the immune response has been studied by several groups. The MEL and amphotericin complex evaluated by Parvez *et al*. showed no toxic effects on J774A.1 macrophages (111). On their part, Laranjeira Silva *et al* demonstrated that, in murine peritoneal macrophages treated for 1 h with 10, 30, or 100 nM of MEL prior to inoculation with L. *amazonensis*, administration of the indoleamine diminished infectivity to about 70%, 4 h post infection, versus vehicle, and the decrease could still be observed 24 h after inoculation (110). Fernandes *et al*. indicated that administration of melatonin to BALB/c macrophages lowered infection by *L. amazonensis*, while modulating the profile of microRNA expression in the host, as well as the production of IL-6, MCP-1/CCL2, and RANTES/CCL9; additionally, MEL increased nitric oxide synthase 2 (Nos2) mRNA expression levels and NO production, altering the macrophage activation state and reducing infection (112). Zamani *et al*. studied the potential effect of changes in the activity of glucose-6-phosphate dehydrogenase (G6PDH) on the resistance of macrophages against *L. major*; thus, after respective *ex vivo* and *in vitro* infection of mouse peritoneal and J774 macrophages with the parasite, and subsequent exposure to 6-aminonicotinamide, a G6PDH inhibitor, or LPS + MEL, an activator, for 24 h, an augmented enzymatic activity in both types of macrophages treated with LPS + MEL was reported, accompanied by meaningful increases in NO production and cell resistance against the protozoan. On the contrary, administration of 6-aminonicotinamide was associated with a notable suppression in the function of G6PDH and synthesis of NO, in tandem with reduced cell resistance against the parasites. It was then conjectured that interfering with the activity of G6PDH activity could affect the leishmanicidal properties in mouse peritoneal and J774

macrophages; therefore, the regulation of G6PDH activity in macrophages could provide a useful window for the development of alternative leishmaniasis therapies (113).

Lastly, the participation of MEL on parasite physiology has been also analyzed. Elmahallawy *et al*. demonstrated that administration of MEL to cultures of *L. infantum* promastigotes decreased the percentage of parasite survival and viability, while also impacting certain mitochondrial parameters, including allocation of intracellular Ca^{2+}, increased mitochondrial nitrite levels and impairment of the respiratory chain complex, effects with potentially lethal consequences for the parasite (114). Further research could help elucidate the participation of the hormone on several parasite processes.

6. ADDITIONAL PARASITIC INFECTIONS: INVOLVEMENT OF MELATONIN

Besides the previously described parasitic infections, the relationship between MEL and other parasites, such as *Giardia lamblia*, *Entamoeba histolytica*, *Trypanosoma brucei*, *Schistosoma mansoni* and *Opisthorchis viverrini* has been studied, although to a far lesser extent. In the case of *G. lamblia*, a leading cause of gastroenteritis throughout the world (115), research has mainly focused on the possible participation of the hormone in the immune response to the parasite, as well as its potential use as an infection biomarker. In effect, Pereira *et al*. studied the content of MEL and cortisol in human colostrum samples, obtained from younger (18 to 35 years old) and older (over 36 years old) lactating women. Samples were further analyzed for immunophenotype, superoxide release, and the assessment of phagocytic rate and microbicidal activity of hormone-treated phagocytes and in the presence of the parasite. In the colostrum of older mothers, the concentration of both MEL and cortisol was higher, along with a lower rate of CD14+ and CD15+ cells, with the indoleamine stimulating the release of superoxide by phagocytes; treatment of both groups with the steroid was associated with greater superoxide levels, in the presence of the protozoan. In older mothers, colostrum mononuclear phagocytes treated with MEL showed higher phagocytosis of the parasite and microbicidal index; mononuclear and polymorphonuclear colostrum phagocytes of younger mothers exhibited higher rates of *G. lamblia* elimination when treated with both MEL and cortisol. The authors concluded that the regulation of the phagocytic activity against the parasite by cortisol and MEL could represent a relevant mechanism for the protection and treatment of parasitic infections in breastfed children (116). Al-Hadraawy *et al*. measured the serum concentration of ghrelin, MEL, glucose and cholesterol in 66 male patients with *G. lamblia* and 30 healthy subjects which served as controls. Overall, results showed that the ghrelin concentration was significantly lower in patients infected as compared to controls, whereas MEL, glucose and cholesterol levels were significantly higher in giardiasis patients as compared to controls. Emphasizing the relatively small number of patients in the study, the authors proposed that the increase in serum MEL levels in the giardiasis group might be explained by the phagocytosis activity; likewise, it was proposed that ghrelin and MEL be used as biomarkers in patients infected (117).

Infections by *Entamoeba histolytica* still represent a serious, worldwide public health problem, notably in developing countries with inadequate access to standard hygienic and sanitary conditions for large swaths of the population (118-120). Although the relationship between MEL and *Entamoeba* infections, particularly *E. histolytica*, has not been sufficiently studied, certain findings support a potential diagnostic and therapeutic role for the indoleamine. In models of amoebiasis, trophozoites of the HM1 virulent strain of *E. histolytica*, were directly injected either into the liver of hamsters or the caecum of Wistar rats; MEL was administered subcutaneously daily; animals were sacrificed on the sixth day after inoculation. In hamsters infected with the parasite, treated with the hormone, hepatic necrosis was significantly reduced when compared with controls; with regards to rats which received the indoleamine, amebic

lesions were reported in just one of six animals. *In vitro*, trophozoite adherence to leukocytes, both mononuclear and polymorphonuclear, as well as the percentage of parasite death during internalization, augmented with the administration of the indoleamine. This protective effect supports the use of the hormone as an adjuvant in the treatment of intestinal and extraintestinal amebiasis (121). In a study with 60 patients of amebiasis and 30 healthy subjects, Al-Hadraawy reported significantly higher serum MEL concentrations, alongside reduced levels of leptin, iron and lactoferrin, in participants infected with the protozoan when compared to controls; the author proposed that the increase in MEL concentrations could be the result of the immune response to the presence of the parasite (122). Further research on the topic will help better understand the effect of MEL on this parasite, and its clinical and therapeutic implications.

The participation of MEL has also been studied in the context of Human African trypanosomiasis, also known as the sleeping sickness, a neglected tropical disease caused by the protozoan *Trypanosoma brucei*; although more research needs to be made in the area, from the results in an animal model of the disorder it was suggested that disturbances in the circadian rhythm involved in the synthesis of MEL might underlie the pathogenesis of the disease (123). Further evaluating the relationship between alterations in the MEL system and the infection by the parasite could open novel, potentially effective clinical options for the treatment of the disease.

Finally, the tissue-protective effect of MEL in animal models of infections by *Schistosoma mansoni* and *Opisthorchis viverrini* encourage the therapeutic benefit of the indoleamine in these infections. According to a model of mice inoculated with *S. mansoni*, the oxidative processes that occur upon infection seem to go uncontrolled, thus contributing to the pathology associated with the infection; results suggested that administration of MEL might be beneficial in the context of this parasitosis, due to the antioxidative properties of the indole (124). In the case of infection by *O. viverrini*, it has been reported that MEL decreases oxidative and nitrosative DNA damage via induction of nuclear erythroid 2-related factor 2 (Nrf2, an antioxidant gene), and inhibits NF-kB mediated pathways in liver tissue of hamsters infected with *O. viverrini* (125), and in a hamster model of cholangiocarcinoma caused by infection with *O. viverrini* with the simultaneous application of the carcinogenic N-nitrosodimethylamine (NDMA), the indole decreased the size of the tumor and improved the survival of the animals (126). The neurohormone was also shown to exert an immunomodulatory effect in another study with the hamster cholangiocarcinoma model, suppressing eosinophils and Th17 cells and the expression of Foxp3, while enhancing CD4+ cells and TNF-α (127), agreeing with previous findings regarding the modulatory actions of MEL on eosinophils (128). The effects of melatonin on parasites are listed in table 1.

Table 1. Relevant findings regarding the relationship between melatonin and parasitic infections

Parasite species	Areas of interest	Relevant findings and effects of melatonin
Plasmodium spp.	Parasite biology	Synchronous maturation of *P. falciparum* and *P. chabaudi* linked with MEL circadian changes (59-62). MEL induces maturation of *P. falciparum* alongside increased expression of the FIS1 and DYN1 genes (76), modifies expression of the protein PfNF-YB, involved in parasitic division (77, 78).
	Diagnosis	MEL increases *P. vivax* and *P. falciparum* detection in blood smears from suspected malaria patients (85).

	Treatment	Suppression of MEL synthesis with bright light at nocturnal hours (68, 69). Inhibition of MEL pathways with indole compounds impairs *P. falciparum* maturation, in infection models (70-74). Anti-apoptotic effects of MEL on mice hepatocytes (82); prevents breakdown of blood-brain barrier and behavioral impairment in *P. berghei*-induced model of cerebral malaria (83).
Trypanosoma cruzi	Parasite biology	Indole synthesized by epimastigotes (86); could accelerate tissue parasite proliferation (97).
	Treatment	In acute infection models, MEL reduces blood trypomastigotes (87); pro-immune and antioxidant effects (88-91). In chronic infection models, MEL improves immune and mitochondrial parameters; antioxidant effects (92-94, 96).
Toxoplasma gondii	Parasite biology	Indole stimulates survival of infected cells (108)
	Treatment	In animas, MEL and/or zinc activate cellular immunity (101); indole reduces parasite proliferation and induces *in vitro* cell death of *T. gondii* (105). In humans, association between recurrent abortions and low serum MEL; administration of indole could prevent risk in pregnant women with acute toxoplasmosis (107).
Leishmania spp.	Physiopathology	In hamsters infected with *L. amazonensis*, MEL in the dark phase decreases parasite replication and lesion evolution (110). MEL in cultures of *L. infantum* promastigotes decreases parasite survival and viability, increases mitochondrial nitrite, and impairs respiratory chain (114).
	Treatment	MEL + amphotericin B reduces intracellular parasite load in liver samples of mice infected with *L. donovani* (111).
Giardia lamblia	Immune response	In lactating mothers, colostrum MEL was higher when protozoan was present; indole increases phagocytic and microbicidal activity of colostrum phagocytes (116).
	Infection marker	Serum MEL significantly higher in patients; might indicate phagocytic activity (117).
Trypanosoma brucei	Physiopathology	Altered circadian rhythm related to MEL synthesis might contribute to human African trypanosomiasis (123).
Entamoeba histolytica	Tissue protection	MEL reduces hepatic necrosis in animals; indole increases trophozoite adherence to leukocytes, and parasite death *in vitro* (121).
	Immune response	Higher serum MEL levels could be indicator of immune response in patients with amoebiasis (122).
Schistosoma mansoni	Tissue protection	MEL might help reduce oxidative damage (124).
Opistorchis viverrini	Tissue protection	MEL decreases oxidative and nitrosative DNA damage, and inhibits NF-kB pathways in hamsters (125); in a parasite-induced cholangiocarcinoma model, indole decreased tumor size and improved survival (126).

MEL: melatonin.

7. CONCLUDING REMARKS

The demonstrated effect of MEL as an immune stimulating factor, both at the cellular and the cytokine level, and the continuing study of the participation of MEL in the biology of different parasite species, keeps opening new doors for research onto solid applications in the context of parasitic diseases. While the actual efficacy of MEL in the treatment of several disorders is still actively debated, and an effective administration regimen must yet be established in humans, it is crucial to reduce chronic or severe complications in parasitic diseases, such as malaria and Chagas disease. Determining the appropriate dosage and combinations for the use of the indoleamine, in well-designed clinical trials, will help improve the lives of people affected by these disorders, particularly in low-income countries, where unhygienic conditions and inadequate access to healthcare contribute to high parasitic infection prevalence.

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AUTHORSHIP

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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