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Potential Relevance of Melatonin Against Some Infectious Agents: A Review and Assessment of Recent Research

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Abstract: Melatonin, a tryptophan-derived neurohormone found in animals, plants, and microbes, participates in various biological and physiological functions. Among other properties, numerous *in vitro* or *in vivo* studies have reported its therapeutic potential against many parasites, bacteria and viruses. In this concern, melatonin was found to be effective against many parasites such as *Plasmodium*, *Toxoplasma gondii*, and *Trypansoma cruzi*, via various mechanisms such as modulation of calcium level and/or host immune system. Likewise, a recent investigation has reported *in vitro* activity of melatonin against *Leishmania infantum* promastigotes which is the causative agent of fascinating visceral Leishmaniasis. This review was initially undertaken to summarize some facts about certain physiological and therapeutic effects of melatonin. It also reviews the effects and action mechanisms of melatonin in bacterial and viral infection besides biology of different parasites which may provide a promising strategy for control of many diseases of public health importance.

Keywords: Bacterial and viral infection, immune system modulation, ion fluxes, melatonin, parasite, therapeutic effects.

1. MELATONIN SYNTHESIS, MAMMALIAN SUBTYPES, PRECURSORS AND THEIR ROLE IN CELL BIOLOGY

Melatonin, N-acetyl-5-methoxytryptamine, is an indoleamine released by the pineal gland with peak concentrations at night and is thought to participate in regulation of circadian rhythms in many eukaryotes, including vertebrates, invertebrates, higher plants and dinoflagellates [1, 2]. Taken into account, the secretion of this natural hormone is not confined exclusively to the pineal gland, but other peripheral organs and tissues including retina, gastrointestinal tract, Harderian gland, skin, leukocytes, thymus and bone marrow cells also produce melatonin but not extrapineal melatonin retains the chronobiotic properties [3, 4].

Melatonin is synthesized from tryptophan and converted into serotonin in the circulatory system [5]. Serotonin is transformed into N-acetylserotonin via arylalkylamine-N-acetyl transferase enzyme which is then metabolized into melatonin by hydroxyindole-O-methyltransferase enzyme [5]. Melatonin is released immediately into the blood capillaries and rapidly distributed throughout the body tissues with high affinity in the cerebrospinal fluid [6], due to its amphiphilic nature which enables it to cross all biologic barriers and gets free access to all cellular compartments, especially nucleus and mitochondria [7].

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To our knowledge, there are two mammalian subtypes of G protein-coupled receptor (GPCR) binds to melatonin receptors; MT1 (Mel1a) and MT2 (Mel1b), which mediate most of the regulatory functions of melatonin [8-10]. Though these receptors mainly expressed in central nervous system (CNS), they also present in peripheral organs [11]. Taken into account, both MT1 (Mel1a) and MT2 receptors are of similar binding properties, however, human MT2 receptor has shown a lower affinity to melatonin *versus* human MT1 receptor [12]. The previously mentioned receptors (MT1 and MT2) seem to be extremely important in regulation of cell cycle in some infectious agents like parasites [13, 14]. Also, melatonin binds to other cellular targets such as calmodulin (CaM), calreticulin, quinone reductase 2 (MT3 binding site), and tubulin, explaining that some effects of melatonin are independent of the activation of membrane-bound receptors [15, 16].

Besides its great role in circadian rhythm, melatonin been implicated in a wide array on the plethora of processes of cell biology and physiological functions in many infectious agents [17-24]. Importantly, the underlying mechanisms of these effects are various and may involve intracellular antioxidant enzymes, receptor-mediated and receptor-independent actions [25]. The following explanation will discuss some physiological and therapeutic implications of melatonin and their potential relevance against some infectious agents (Fig. **1**).

2. PHYSIOLOGICAL AND THERAPEUTIC EFFECTS OF MELATONIN

2.1. Effects of Melatonin on Immune System

Melatonin has been recognized as neuroendocrine–immunological network modulator due to its affinity to T-lymphocytes (CD4+) and innate immunity [26-29]. Several previous studies have reported the immunomodulatory effect in both animals and humans as it enhances innate and acquired immunity through activation of natural killer (NK) cells and antibody-dependent cell-mediated cytotoxicity and subsequently increases T cells proliferation and production of cytokines [26, 30-33]. This may justify the immunotherapeutic potential of melatonin which counteracts the induced-immunosuppression by acute stress, ageing, bacterial and viral infections [27, 34, 35].

As previously mentioned, leukocytes, bone marrow cells, thymocytes and epithelial cells have been reported to produce melatonin [3, 36, 37]. Even more, cultured human lymphocytes were able to release large amount of melatonin which has autocrine, endocrine, intracrine, and/or paracrine effects, and therefore coordinates immune response [31]. The presence of melatonin's receptors (especially MT1) in different immune cells of thymus and spleen also implicates the modulatory and anti-inflammatory effects of melatonin [7, 38]. These effects are mainly mediated through its effect on certain receptors in immune organs and immunocompetent cells of many mammals, as well as human [39-41]. The involvement of receptors MT2 in melatonin's modulatory effects have been explored in mice through enhanced splenocyte and lymphocytes proliferation, while this effect was blocked by the MT2 antagonist luzindole [26, 37, 42-44].

Melatonin also regulates hematopoiesis indirectly through its action on certain receptors located on bone marrow cells and via the induction of T-helper-cell-derived opioid cytokines [45], or directly through its action on some progenitor cells such as NK cells, pre-B cells, and monocytes [46, 47]. Hence, the anticancer action of melatonin may be attributed to activation of lymphocytes, monocytes and macrophages which also prevents tumor development [48, 49]. Likewise, activation of melatonin receptors has been reported to enhance the secretion of cytokines by T-helper cell Type 1 (Th1), like interleukin-2 (IL-2) and gamma-interferon (IFNc) [30, 37, 45]. Interestingly, activation of T-helper cells type 1, monocytes, and/or monocyte-derived cells by melatonin was found to enhance the production IL-1, IL-6, IL-12, IFN-γ, and macrophage-colony stimulating factor (M-CSF), which together act through binding to nuclear RZR/ROR receptors subfamily belongs retinoic acid receptor and membrane MT1 and MT2 receptors [9, 46, 50-52]. These previously mentioned cytokines may counteract stress-induced immunosuppression in several infectious cases [46], besides their role in immunomodulation process [28].

Melatonin also promotes the expression of major histocompatibility complex (MHC) class II and transforming growth factor (TGF)-β in antigen-presenting cells (APC) [30, 53]. In addition to promotion or suppression of Th-2 responses in some cases, melatonin involved in down-regulation of cyclooxygenase expression in macrophages and 5-lipoxygenase which antagonizes prostaglandin synthesis [3, 27, 34, 35].

On the other hand, the role of melatonin in other autoimmune diseases is still controversial and the mechanism of action is poorly understood, however, some studies related such effects to the balance between Th1/Th2 and others suggest its contribution to the immune system homeostasis [46, 54]. In this regard, this compound has pro-inflammatory action in

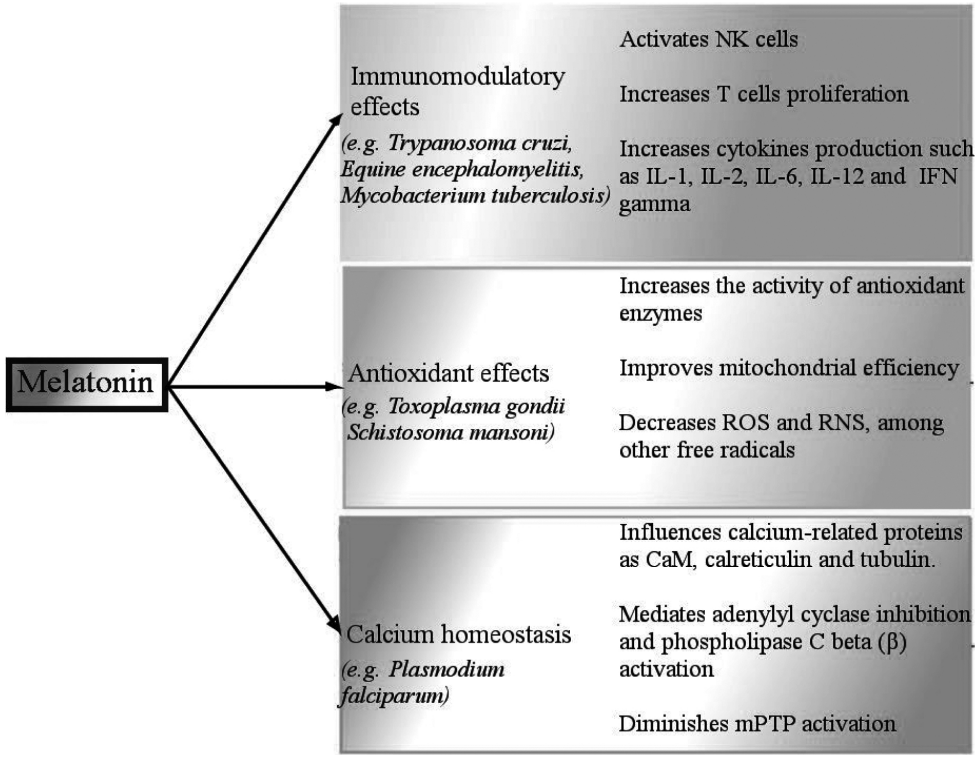

Fig. (1). Summarize the physiological and therapeutic implications of melatonin and their potential relevance against some infectious agents [14, 19, 30, 32, 34, 35, 37, 46, 50, 52, 59, 60, 61, 135, 142, 144, 165, 180, 197].

rheumatoid arthritis patients where a high plasma level of melatonin was found and the synovial macrophages of the patients respond to exogenous melatonin with an increased production of IL-12 and nitric oxide (NO) [53, 55]. Hence, melatonin antagonists may achieve therapeutic effects in such cases and further studies are necessary to understand the underlying mechanisms of action [54].

2.2. Antioxidant Action of Melatonin

Oxidative stress is a common term refers to the disturbance in the balance between the reactive oxygen species (ROS) and the antioxidant defense [56] which accompanied several pathological conditions such as parasitic infection and aging [57, 58]. Based upon several published works, melatonin has shown a potential antioxidant effect resulted from both hydrophilic and hydrophobic features of this indolamine that allow it to cross several body barriers [59]. Also, melatonin indirectly regularizes the activity of several antioxidant enzymes, increases the efficiency of mitochondrial bioenergetics, and reduces the electron leakage from the mitochondria, which in turns lowers the free radical generation and augments the efficiency of other antioxidants [60-62]. Additionally, melatonin has a great scavenging activity for the free radicals, including hydroxyl radicals like hydroperoxyl radical, NO, singlet oxygen or peroxynitrite anion ($ONOO^-$), which explains the role of melatonin as a potent scavenger of mutagenic and carcinogenic hydroxyl radical ($OH^{\bullet}$) [7, 60]. Interestingly, this anti-inflammatory action of melatonin results from its inhibitory effect on inducible nitric oxide synthase (NO synthase), which consequently reduces the oxidative damage and protects from NO-mediated mitochondrial blockade under acute or chronic conditions [36, 37, 63-65]. Hence, some clinical trials suggested that melatonin can contribute efficiently to several metabolic functions [66].

2.3. Role of Melatonin in Bacterial and Viral Infection

Several published works have reported the beneficial effect of melatonin in bacterial and viral infections [29, 34, 67, 68]. Indeed, administration of melatonin was found to be effective in controlling chlamydial and bacterial infection caused by *Mycobacterium tuberculosis*, *Helicobacter pylori*, and *Dichelobacter nodosus*, in addition to many viral infections such as *Equine encephalomyelitis* virus and *Ebola* virus disease [34, 68-74]. The activity of melatonin in these cases is mainly attributed to its free radical scavenger activity, regulation of bacterial growth, depletion of some intracellular

substrates like iron, and/or immunomodulatory-adjuvant activities [72, 75-77].

2.4. Melatonin and Parasites

General remarks about role of calcium homeostasis in biology of some parasites and its relation to the anti- parasitic effects of melatonin.

In fact, the cell function in parasites is coordinated using a second messenger signaling cascades involving cyclic adenosine monophosphate (cAMP) and calcium (Ca^{2+}) [78-88], which control many critical events including host cell invasion, gliding motility, parasite differentiation and egress [89-97]. Even more, calcium binding proteins such as CaM and calcium-dependent protein kinase (CDPK) genes play critical roles in protein secretion, host cell invasion and parasite differentiation [94, 98]. Calmodulin (CaM), the ubiquitous intracellular calcium binding natural regulator, has been identified in American and African trypanosomes, *Leishmania braziliensis*, *Leishmania mexicana* and *Leishmania donovani* [99-101]. It shared 99% amino acid sequence identity between trypanosomatids [99-101] and related to various functions in trypanosomatids like cAMP-dependent phosphodiestherase stimulation in *Trypanosoma cruzi (T. cruzi)* [102-104], Ca^{2+}/calmodulin (Ca^{2+}/CaM)-dependent protein kinase (TcCaM K) [105, 106], and transduction mechanisms of the cGMP-nitric oxide pathway in *T. cruzi* [107-109]. These events allowed CaM to act as: a mediator of Ca^{2+} functions, calcium sensor, and signal transducer to many proteins which are able to bind to CaM and unable to bind calcium [110].

Moreover, some scientists have reported other important functions of Ca^{2+} in regulation of cellular differentiation, cAMP levels in *T. brucei* [111-113], and cAMP phosphodiesterase in *T. cruzi* [103, 114]. It was also proposed that inositol 1, 4, 5-trisphosphate (InsP3)- dependent calcium response in Plasmodium species (spp.) and *T. gondii* [115]. Calcium is also considered the main controller of protein secretion, invasion, motility, and egress of *Toxoplasma* [116, 117], while it is very critical for developmental regulation and cyclic nucleotide signaling in *Plasmodium* with involvement of many stages of invasion and motility of the parasite including erythrocyte invasion stage by merozoites [118], besides its important role in the sexual multiplication in the mosquito vector [119-124].

Similar to eukaryotic cells, intracellular Ca^{2+} is finely regulated in trypanosomatids by various organelles [90, 109, 125], including mitochondria, endoplasmic reticulum, Golgi and acidocalcisomes which are known as major calcium storage sites [109, 126]. Moreover, trypanosomatids possess acidocalcisomes which involved in bioenergetics besides a single mitochondrion which represents 12% of the parasite volume and capable for accumulation large amounts of polyphosphates together with Ca^{2+} ions [127-129]. Accordingly, any fluctuations in cytosolic Ca^{2+} level ($[Ca^{2+}]i$) could control many cellular functions in such organisms [91, 94]. In this regard, many of available antiprotozoal agents exert their effects through alteration of Ca^{2+} homeostasis in the parasite and/or through impairment of the activity some mitochondrial parameters [130, 131].

According to the latest publications, melatonin has shown a wide range of activity against various parasites [68, 132]. To our knowledge, the signal transduction mechanisms of melatonin for its receptors are different among the various tissues and cell types [23, 133, 134]. It has been reported that melatonin exerted its effects in such pathological conditions through its influence on some intracellular proteins like CaM [135, 136], calreticulin [137], or tubulin [138], antagonizing the binding of Ca^{2+} to CaM [139]. As mentioned above, there are two mammalian subtypes of G protein coupled heterodimers participate in signaling pathways, leading to downstream effects on Ca^{2+} channels, Ca^{2+} signaling and changes in extracellular-signal-regulated kinases which give melatonin and its derivatives a pleiotropic nature [3, 140, 141]. MT1 melatonin receptor could also mediate adenylyl cyclase inhibition and phospholipase C beta (β) activation through its coupling to different G proteins. Therefore, activation of MT1 receptor may activate a large variety of G proteins which inhibit the cyclic adenosine monophosphate (cAMP) signal transduction cascade and their accumulation decrease the activity of protein kinase A and cAMP response element binding CREB) [142-144]. Melatonin (MT1) receptors also regulate ion fluxes besides their influence on calcium-activated potassium channels [145-147]. Likewise, several studies have reported a numerous safeguarding mitochondrial effects of melatonin, which is mainly attributed to its role on respiratory electron flux [7, 31] or through its unique effect in alteration of Ca^{2+}-induced mitochondrial permeability transition pore (mPTP), which is found to be a gatekeeper of apoptotic and necrotic cell death [3, 14].

Taken together, these previous events have a strong influence on the control of some infectious agents, especially the parasitic type, since disruption of Ca^{2+} homeostasis may result in cell death [137], however, it should be borne in mind that the suggested mechanisms

underlying this activity seem to be different among these parasites (Fig. **2**). The following section will highlight several facts about the potential activity of melatonin against several global infectious diseases caused by a group of parasites.

2.4.1. Melatonin and Apicomplexa

2.4.1.1. Melatonin and Malaria

Malaria is mosquito-borne infectious disease of humans and other animals caused by protozoan of genus *Plasmodium* and mainly transmitted via the bites of infected mosquitoes [148]. More than 220 million cases of malarial infections are reported every year, and the disease kills between 473,000 and 789,000 people worldwide, mainly in Africa [50, 148, 149]. *Plasmodium falciparum* (*P. falciparum*), *Plasmodium malariae* (*P. malariae*), *Plasmodium vivax* (*P. vivax*), *Plasmodium knowlesi* (*P. knowlesi*) and *Plasmodium ovale* (*P. ovale*) are the main causative species [148, 149]. The parasite multiplies in the liver of human, and then infects red blood cells (RBCs); this stage (erythrocytic) occurs after 48 hours in *P. falciparum* and consists of ring, trophozoite, schizonts and ultimately give rise to merozoites that release into the blood stream at a specific time of the day-night cycle [51].

Melatonin and its precursors are widely known as a nocturnal signal can regulate the cell physiology of the parasite, besides their critical role in the synchronization of maturation of the parasite and its survival in the host [20, 36, 52, 150, 151]. In this regard, several studies have reported that melatonin drives a temporal regulation in some species of *Plasmodium* either *in vivo* or *in vitro* [14, 152]. Importantly, melatonin drives as a second messenger through modulation of Ca^{2+} and cyclic-AMP pathways, besides its role in activation of Protein kinase A (PKA), a class of cAMP-dependent enzymes which modulates the cell cycle [151, 153]. The level of extracellular calcium is a critical event for the invasion of the parasite into RBCs, exflagellation process as a step of sexual stage of the life cycle, and *Plasmodium* kinases [154-156]. Indeed, melatonin and its derivatives promote $[Ca^{2+}]i$ increase by mobilizing it from internal stores either by direct uncaging (Photolytically) of $InsP_3$ within the intraerythrocytic stage of the parasite or by increasing parasite inositol phosphate formation, which subsequently modulate the *P. falciparum* cell cycle [24, 157, 158]. Therefore, they could regulate and modulate the life cycle of human malaria parasite, *P. chabaudi* and *P. falciparum*, *in vivo* and *in vitro* [24, 151], by mobilization of Ca^{2+} from internal Ca^{2+} pools of parasite trophozoite, augmenting the proportion of schizonts and cytosolic free Ca^{2} [150].

Furthermore, recent studies have revealed that melatonin up regulates the genes related to ubiquitin-proteosome-protein system (UPS) which involved in specific functions related to pathogenesis and virulence of *P. falciparum* [22, 159]. It should be also pointed out that exogenous melatonin remarkably prevents development of mitochondrial pathology and mitochondrial oxidative stress in hepatocytes, which in turns prevents hepatic cell damage resulting from malaria infection [151, 160, 161].

On the other hand, melatonin is known as a potent antioxidant agent protects malarial parasites from ROS attacks in the oxygen rich environment at erythrocytic stage [161, 162]. Arguably, the blockade of melatonin's nocturnal action on malaria parasite growth or the circadian changes in the melatonin levels of the host using common melatonin antagonists or some derivatives seems extremely important in combating this disease [129, 158]. Taken these facts together, melatonin and its derivatives exhibit potent antimalarial effects.

2.4.1.2. Melatonin and Toxoplasmosis

Toxoplasmosis is a worldwide parasitic zoonotic disease caused by protozoan of genus *Toxoplasma gondii,* which is considered a causative agent of death in the United States [163]. Most warm-blooded animals can be infected, including humans, but the primary host is family Felidae [163].

Several studies have investigated the effect of artificial supplementation of melatonin and/or zinc on the response of immune system to *T. gondii*. Melatonin has shown an important role in activation of cellular immunity by stimulating $CD4^+$ and $CD8^+$ production [68, 164-166]. Furthermore, NO levels increase in *Toxoplasma* infection, particularly in the chronic phase of the infection in Sprague-Dawley rats, which increases in melatonin deficiency. Hence, melatonin reduces the activity inducible nitric oxide synthase (iNOS) activity which enhance the immune system by the activation of Astrocytes and HUVEC cells, resulting in NO release in the presence of the parasite and the later might be beneficial to the host, as it normalizes nitrites (NO_2^-) levels [167, 168]. Taken together, melatonin could be an adjunctive therapy for treatment of *Toxoplasma* retinochoroiditis, especially in immunosuppressed individuals.

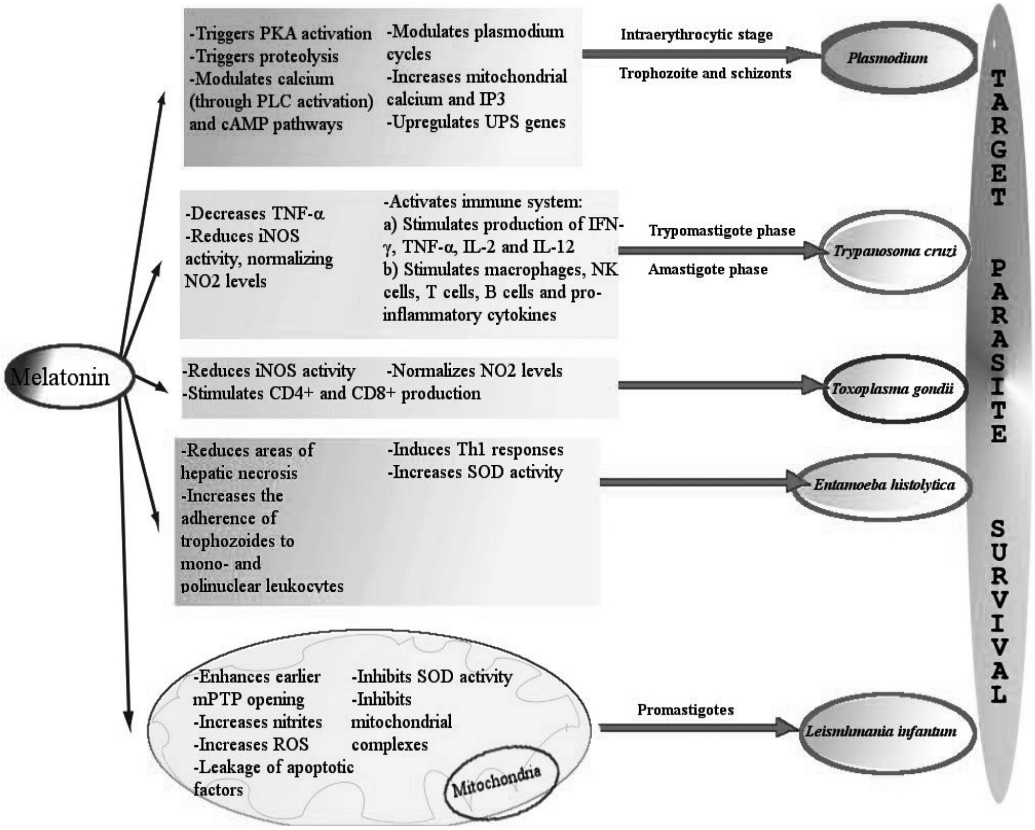

Fig. (2). Summarize the action of melatonin with *Plasmodium*, *Toxoplasma gondii*, *Trypansoma cruzi, Entamoeba histolytica*, and *Leishmania infantum* promastigotes [19, 22, 24, 68, 150, 151, 153, 157, 168, 179, 183, 185, 186, 200, 210].

2.4.2. Melatonin and Trypanosomasis

Trypanosomiasis is a group of parasitic diseases of vertebrates, mainly caused by protozoan parasite of genus *Trypanosoma*. The parasite has three different stages: trypomastigote, amastigote, and epimastigote [169]; the transformation of epimastigote form into the metacyclic trypomastigotes is mainly occurred during darkness period [170].

There are two main forms of Trypanosomiasis; Human African Trypanosomiasis which is common disease in 36 countries of sub-Saharan Africa with more than 60 million people at risk [171] and is caused by *Trypanosoma bruceigambiense* or *Trypanosoma bruceirhodesien*se while tsetse flies are responsible for transmission of the disease to human [172]. The other form, American trypanosomiasis (Chagas disease), is caused by *Trypanosoma cruzi* (*T. cruzi*) and transmitted mostly by insects known as Triatominae [173], resulting in 21,000 cases of deaths annually, mainly in Latin America [173]. Sudden death in acute patients may be resulted from congestive heart failure associated with myocarditis or meningoencephalitis [174], while most of the patients develop the chronic form of the disease [175].

Several studies have reported the significant contribution of melatonin in controlling *T. cruzi* multiplication *in vivo* and *in vitro* [176-178]. In this regard, melatonin treatment (5 mg/kg orally), prior to experimental infection or during the infection, resulted in reduction of the levels of IL-10, IL- 4, tumor growth factor-β and NO, while it increased the number of macrophages and enhance the release of IL-12, IL-2, TNF-α and IFN-γ [19, 179-181]. In such cases, melatonin up-regulates Th-1 immune response and suppressed Th-2 response [19, 182, 183], which promotes a reduction in blood and tissue parasites, and therefore reduce the parasitemia combined with the blockade of prostaglandin E2 synthesis [21, 184].

Administration of melatonin during the acute phase of infection with the parasite may possess a dual effect (promoting and inhibitory) on *T. Cruzi* life cycle, based upon the period of exposure and the concentration used [184, 185]. In this regard, melatonin administered during the acute phase of *T. cruzi* infection resulted in reduction of the parasitemia [178], inhibition of parasite

propagation or killing the parasite through its action on the immune system, as it activated the macrophages as a result of enhanced NO production. This later product is considered the major effectors' molecule of *T. cruzi* intracellular amastigote killing [176, 186, 187]. It has also been proposed that ROS and oxidative stress play an important role in expansion of the systemic complications of Chagas, especially cardiomyopathy [188-191]. As consequences, mitochondrial functional decline, combined with loss of the scavenger activity for ROS, resulting in sustained oxidative stress during infection [189, 190]. Furthermore, NO accumulation was found to slow down the electron transport chain, which inhibits the production of Adenosine triphosphate (ATP), higher ROS production, and in turn increases the susceptibility of cell death [192]. Indeed, melatonin could protect mitochondria by counteracting the oxidative damage and prevent the development of heart damage [193].

During the chronic phase of the disease, melatonin could be beneficial for combating the disease progression [189, 194]. It could reduce the oxidative stress accompanying the myocardial damage, which represented by reduction in the number of trypomastigotes, fewer amastigote carriage, lower tissue disorganization in the heart, and higher number of leucocytes resulted from activation of Th-1 inflammatory response [19, 178, 185]. Therefore, administration of melatonin agonist like the MT1/MT2 agonist (ramelteon) in Chagas´ disease during the acute phase may enhance the immune response without impairment in NO production, while high doses of melatonin during the chronic course of the disease lowers the oxidative stress, preserves the mitochondria and prevents the development of cardiomyopathy [194]. These findings prove that melatonin either alone or in association with other drugs such as meloxicam could be helpful therapy in American trypanosomiasis [19, 178].

2.4.3. Melatonin and Schistosomiasis

Schistosomiasis (Bilharzia) is neglected disease caused by parasitic worms of genus *Schistosoma* [195]. The disease affects almost 210 million people worldwide [195] and is considered the second devastating parasitic disease after malaria, especially in poor societies with unclean water and inadequate sanitation [196].

Melatonin enhanced the protective immune response against *Schistosoma mansoni* in hamster infected with *Schistosoma mansoni* using cercarial and soluble worm antigens [18]. Indeed, melatonin has been postulated to be protective against the pathological changes in *Schistosoma mansoni*-infected mice, which may be resulted from its antioxidant and free radical scavenging activity that reduces the oxidative damage and increases the survival rate [197].

2.4.4. Melatonin and Amoebiasis

Amebiasis is a parasitic infection of the large intestine, sometimes involving the liver caused by *Entamoeba histolytica,* and estimated to cause 70,000-100,000 deaths per year worldwide [198, 199]. França-Botelho and co-authors have studied the effect of melatonin administration (15 mg/kg body weight subcutaneously) in experimental amoebiasis (*in vivo* and *in vitro*) and on the relationship between trophozoites of the virulent strain HM1-IMSS of *E. histolytica* and human blood cells [200]. They have noticed a marked decrease in the amoebic necrotic areas in liver infiltrated with large quantities of mononuclear inflammatory cells, which explains the enhanced adherence of the parasite trophozoites to mononuclear and polymorph nuclear leukocytes (PMN) [68, 200]. Therefore, melatonin administration resulted in induction of Th1 responses and could establish its role as an adjuvant therapeutic agent in amebiasis [68, 200].

2.4.5. Melatonin and Leishmaniasis

Leishmaniasis is a group of neglected diseases, caused by infection by flagellate protozoa of the genus *Leishmania* and present in all inhabited continents with a clear endemicity in tropic and subtropics areas [153, 201]. Transmission of the infection to human occurs through a biological vector (Insecta, *phlebotomine* sand fly) and the parasite has two different stages; an extracellular form (promastigotes) in the insect midgut and an intracellular form (amastigotes) inside the infected macrophages. The last years have witnessed extraordinary expansion of the disease to be endemic in 98 countries around the world and 60.000 mortality cases every year [201, 202]. There are three forms of human Leishmaniasis: (i) Cutaneous Leishmaniasis (CL), (ii) Mucocutaneous Leishmaniasis (MCL), and (iii) Visceral Leishmaniasis (VL) [162, 203, 204]. VL caused by *Leishmania donovani* complex (*L. donovani*) in Africa, India, and Asia; by *Leishmania chagasi* in America; and by *Leishmania infantum* in Europe [204, 205].

Despite several leishmanial researches, a limited number of effective and less toxic antileishmanial agents are available which is mainly encountered by the development of drug resistance [206, 207]. As previously mentioned, *Leishmania* is a member of the trypanosomatidae family possess a large mitochondrion

which represents 12% of the parasite volume and can accumulate large amounts of Ca^{2+} [129], besides its role as in important target for many of the available antileishmanial agents [130, 208, 209]. Recently, melatonin has shown antileishmanial activity against the promastigote phase of *Leishmania infantum*, together with marked alteration in parasite mitochondrial calcium level and significant alteration in some mitochondrial parameters, and therefore target parasite survival [210].

CONCLUSION

Melatonin is a naturally occurring compound can participate in various biological and physiological functions. It has also been proposed not only in alternative medicine for treatment many degenerative and inflammatory diseases but also as an adjuvant candidate with a good pharmacological safety profile in many infectious diseases. Among other parasites, melatonin has shown inhibitory effect against *Plasmodium falciparum*, *Trypansoma cruzi*, *Schistosoma mansoni*, *Toxoplasma gondii*, *Entamoeba histolytica*, and recently *Leishmania infantum* promastigotes. The activity of melatonin against these parasites is mainly attributable to its immunomodulatory effect, antioxidant effect and/or regulation of ion fluxes mainly calcium, potentiated by its receptors in different organs. Further future research is warranted to elucidate the other effects of melatonin either alone and/or in association with the other available antiparasitic agents. Employing these effects in clinical trials for treating infected patients could be promising not only for the patients infested with the disease but also in prevention of these diseases.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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