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Vorinostat as potential antiparasitic drug

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Abstract. – OBJECTIVE: Vorinostat is a drug used to treat cutaneous T cell lymphoma whose action mechanism is based on Histone Deacetylase inhibition. Histone Deacetylases are a family of enzymes that remove acetyl groups from histone and non-histone proteins that control many crucial processes, such as gene regulation, cell cycle progression, differentiation, and apoptosis. Histone Deacetylase homologues are also expressed in parasites of the genus *Plasmodium, Leishmania, Cryptosporidium, Schistosoma*, Entamoeba, and others. In this way, antiparasitic properties of Vorinostat have been explored. The aim of this review is to report the current state knowledge of Vorinostat as antiparasitic drug against *Plasmodium*, *Leishmania, Cryptosporidium, Schistosoma* and *Entamoeba* in order to support future investigation in this field.

MATERIALS AND METHODS: The authors revised the recent and relevant literature concerning the topic and discussed advances and limitations of studies on Vorinostat as potential drug to treat human parasitic diseases.

RESULTS: Vorinostat has been efficient *in vitro* and, in some cases, *in vivo*, against parasites that cause parasitic diseases, such as malaria, leishmaniasis, cryptosporidiosis, amoebiasis, and schistosomiasis.

CONCLUSIONS: *In vitro* and *in vivo* models have demonstrated the antiparasitic activity of Vorinostat, however, the challenge is to assay its activity in animal models and to evaluate if Vorinostat is safe for humans as new alternative to treat human parasitic infections.

Key Words:
Vorinostat, Antiparasitic drug, Histone Deacetylase inhibitor.

Introduction

Parasitic diseases, such as malaria, leishmaniasis, cryptosporidiosis, amoebiasis, and schistosomiasis affect millions of people worldwide and are an important cause of morbidity and mortality, especially in developing countries[1,2].

The development of a new antiparasitic therapy is urgently needed because the drugs used for treating these diseases were introduced decades ago and resistance and side effects to these drugs have been reported[3,4]. Furthermore, the high cost and extended periods of time needed to discover novel antiparasitic molecules, and researching of new uses of existing drugs is an opportunity for the antiparasitic drug therapy[5,6].

Vorinostat is an approved drug by Food and Drug Administration, and it is used to treat the cutaneous T cell lymphoma; its mechanism of action is based on the Histone Deacetylase (HDAC) inhibition[7]. Parasites of the genus *Plasmodium*, *Leishmania*, *Schistosoma*, and others express HDAC homologues; consequently, Vorinostat has been studied as an antiparasitic drug against them[8]. Here, we review the current studies performed to analyze the role of this Histone Deacetylase inhibitor as an antiparasitic drug.

Mechanism of Action of Vorinostat

HDACs are a family of enzymes responsible for catalyzing the removal of acetyl group from the lysine residues of histone tails resulting in a more condensed chromatin, which is a transcriptional regulation mechanism (Figure 1)[9]. As

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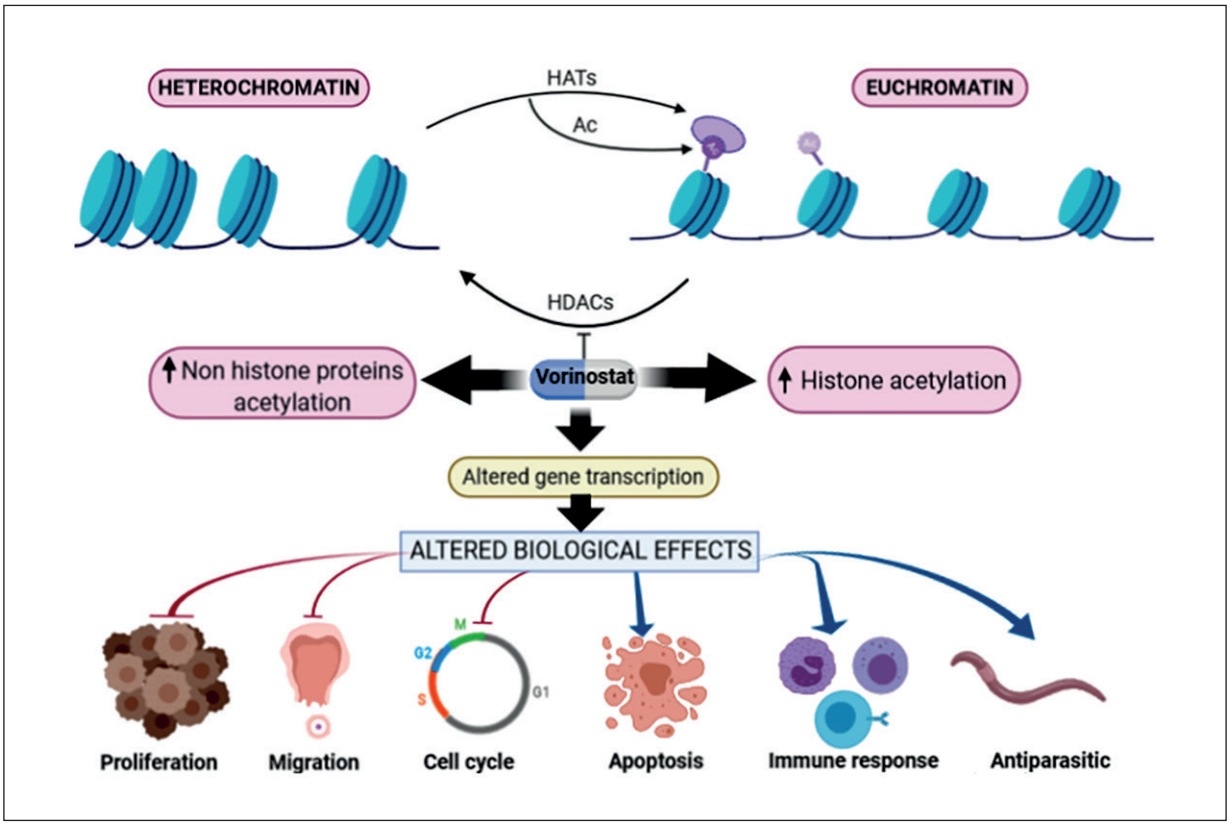

Figure 1. Overview of the biological effects of Vorinostat. Schematic representation of the molecular pathways involved in HDAC inhibition by Vorinostat. The acetylation status of histones is regulated by the opposing action of Histone Acetyl transferases (HATs) and Histone Deacetyl transferases (HDACs), Vorinostat inhibits HDACs and induces hyperacetylation both histone and non-histone proteins which leads to altered gene transcription that cause inhibition of cell proliferation, cell migration, and cell cycle, and induces apoptosis and immune regulation. Furthermore, parasite growth is also inhibited by hyperacetylation of histones induced by Vorinostat.

well as the histone proteins, HDACs have also non-histone protein substrates, such as structural proteins, chaperones, mediators of signaling, and transcription factors; thus, the HDACs can regulate cell proliferation, migration, apoptosis, immune function and angiogenesis[10-12].

HDACs are the target of some drug inhibitors to treat certain human diseases with acceptable side effects[13]. HDACs are classified in four classes based on their protein sequence similarity and cofactor dependence: the classes I, II and IV are zinc-dependent enzymes, and class III differs with the other HDACs by using NAD^+ as cofactor[14].

HDAC inhibitors commonly target the zinc dependent HDAC enzymes[15]. Vorinostat, which is used to treat cutaneous T cell lymphoma, inhibits class I (HDAC1, HDAC2, HDAC3, HDAC6 and HDAC8) and class II HDACs (HDAC4, HDAC7, HDAC9)[16-18].

Vorinostat has a small molecular weight (264.32 g/mol) and its structure is $C_{14}H_{20}N_2O_3$ (Figure 2), these characteristics allow its binding to zinc atom in the catalytic domain of HDACs enzymes and to project their phenyl ring out of the catalytic site onto the surface of HDAC enzymes (Figure 3), thus HDACs cannot remove the acetyl group of histone and non-histone proteins provoking accumulation of acetylated proteins with effects in

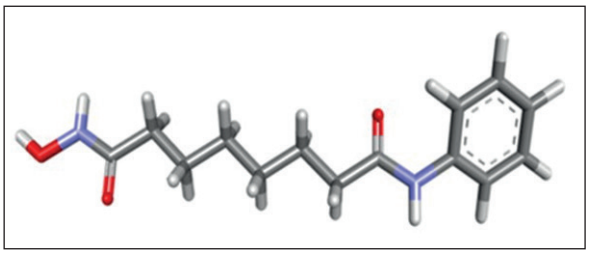

Figure 2. Structure of Vorinostat.

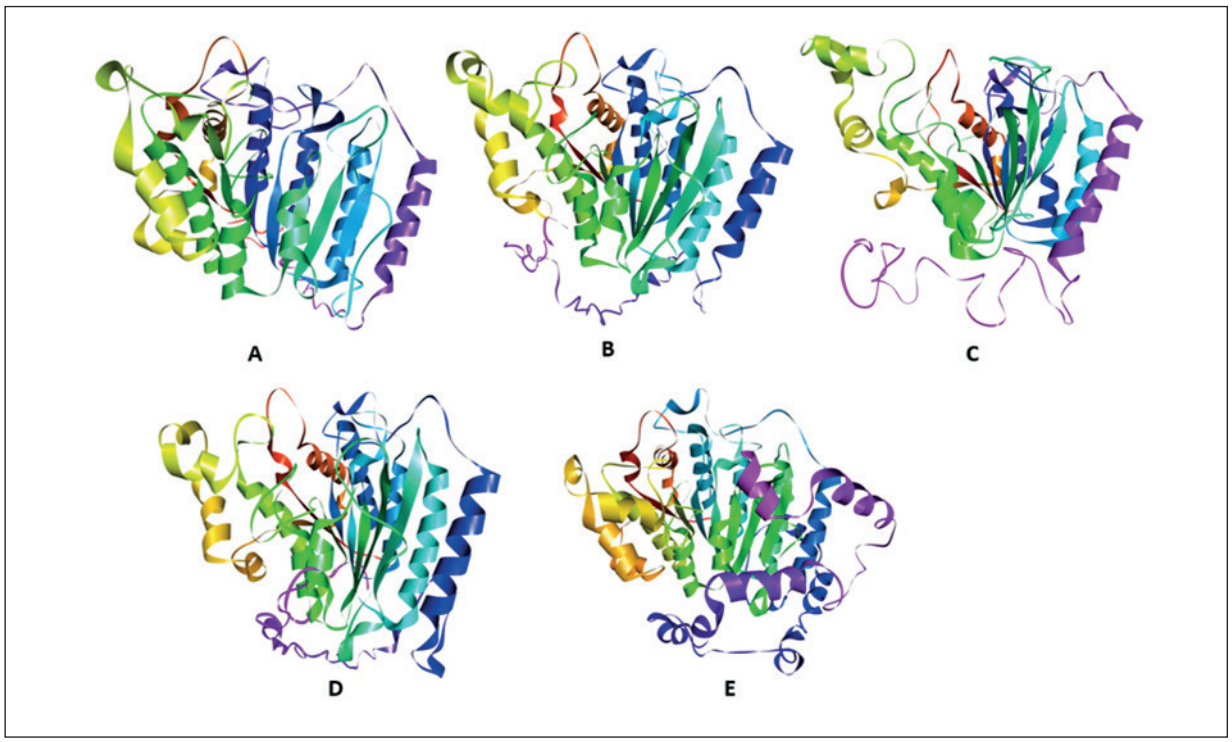

Figure 3. Homology modeling of parasites Histone Deacetylases. **A,** Histone Deacetylase of *Plasmodium falciparum* (PfHDAC1). **B,** Histone Deacetylase of *Criptosporidium parvum* (CpHDAC3). **C,** Histone Deacetylase of *Entamoeba histolytica* (EhHDAC). **D,** Histone Deacetylase of *Plasmodium falciparum* (PfHDAC1). **E,** Histone Deacetylase of *Schistosoma mansoni* (SmHDAC8).

many cellular functions, such as cell cycle arrest, as it has been demonstrated in cancer cells[18,19] and probably in parasites. Vorinostat can act directly or indirectly on transcriptional factors as E2F-1, YY-1, Smad 7, p 53, Bcl-6 and GATA-1 that affect cell cycle progression, apoptosis and immune response through the regulation of genes related to these processes (Figure 1)[20-24].

Pharmacokinetics of Vorinostat

Vorinostat administered in a dose of 400 mg shows a half-life (t 1/2) of 60-100 minutes and a maximum concentration (C_{max}) of 90 minutes[25,26]. The metabolism and elimination of Vorinostat, as well as its metabolites (Vorinostat-O-glucuronide and 4-anilino-4-oxobutanoic acid), are mainly given by glucuronidation, hydrolysis, and beta-oxidation. Glucuronidation is catalyzed by the UDP-glucuronosyltransferases (UGTs), specifically: UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B17; the renal excretion of the drug and its metabolites have been obtained from urine with the following percentages: 1% as drug without changes, 12-23% as O-glucuronide metabolite and 41-63% more as 4-anilino-4-oxobutanoic acid[27,28]. *In vivo* and *in vitro* studies[29] indicate that Vorinostat is not metabolized by the cytochrome p450 system.

Adverse Effects

Vorinostat is well tolerated at an oral dose 400 mg/d, however, side effects are common but mild to moderate severity. Common side effects include nausea, fatigue, fever, diarrhea, anemia, neutropenia, thrombocytopenia, decreased appetite, among others[30]. The US Food and Drug Administration has assigned this medication to pregnancy risk category D. Hepatotoxicity in association with Vorinostat has not been reported[18,31].

Vorinostat as Antiparasitic Drug

HDACs are targets for cancer therapy but they have been also explored in parasitology to develop new antiparasitic drugs[8,32]. Some HDAC homologues (Figure 3) have been described in parasites and play a crucial role in gene expression and survival of parasites, they are emerging as a potential antiparasitic target.

Several studies have explored the antiparasite effect of specific HDAC inhibitors, such as cyclic tetrapeptide, short chain fatty acids and hydroxamate HDAC inhibitors[8,33,34]. Vorinostat is a synthetic compound derived from hydroxamic acid and, approved in 2006 for clinical use in treating cutaneous T-cell lymphoma, and is also the most studied antiparasitic HDAC inhibitor[35]. *In vitro* and *in vivo* models have demonstrated the antiparasitic activity of Vorinostat.

Malaria

Plasmodium spp. is a unicellular protozoan that causes malaria, a major cause of death and morbidity worldwide[36]. Malaria is acquired when an infected mosquito injects sporozoites to a healthy person. Sporozoites migrate to the liver and invade hepatocytes, where they multiply and differentiate into schizonts. Subsequently, schizonts are released into the blood, where they invade and replicate in red blood cells[37].

Treatment with antimalarial drugs (Quinine, Chloroquine, Artemisinin, Artesunate, Cipargamin, Primaquine) depends on the severity of the disease, the *Plasmodium* species and drug resistant strains[38]. One disadvantage of these drugs is that when it is used as monotherapy, there is increased risk of drug resistance, in addition to the side effects, such as acute hemolytic anemia, maculopathies, fever and renal failure when it is used for extended periods of time or at higher doses[39,40].

In *Plasmodium falciparum,* one of the most prevalent malaria parasites, some HDACs have been identified: pfHDAC1, a homolog protein of class I HDACs human; pfHDAC2 and pfHDAC3 are homologs proteins of class II HDACs human; pfSir2A and pfSir2B are homologs proteins to class III HDAC human[41,42].

PfHDAC1 has a high homology to human class I HDACs, nevertheless, the biological functions of PfHDAC1 have not been fully characterized[43]. Using HDAC inhibitors, it has been established that PfHDAC1 is involved in regulating the gene expression and survival of *Plasmodium*[44].

In vitro analysis has shown that Vorinostat at nanomolar concentrations inhibits *Plasmodium falciparum* and *Plasmodium knowlesi* growth[8]. Histone hyper-acetylation is also observed in Vorinostat treated-*Plasmodium* compared to no-treated parasites, indicating that growth inhibition is related to acetylation, which is affected by Vorinostat. *In vivo* studies showed that Vorinostat (25 mg/kg) has a significant effect in the parasitemia development, showing a reduction and delay in parasitemia progression in mice orally treated with Vorinostat, compared with control mice treated with vehicle. On the other hand, Chua et al[8] concluded that Vorinostat has a limited anti-*Plasmodium* activity compared with panobinostat, another potent HDAC inhibitor, however, this would be difficult to justify as treatment against malaria due to its side effects produced by the high dose needed to be used as an antimalarial. Vorinostat has been structurally modified to improve HDAC selectivity, thus Vorinostat-like molecules should be tested against *Plasmodium* to evaluate the antiparasitic activity[45].

Leishmaniasis

Leishmania is an obligate intracellular protozoan; it is the causal agent of an endemic disease known as leishmaniasis, which is more common in tropical developing countries[46]. This parasite is transmitted when female sand flies are infected with the promastigote form, which is injected into the human and subsequently phagocytized by macrophages and transported to the reticuloendothelial system where they are transformed into intracellular amastigotes; after that, they infect other cells[47].

There are many antiparasitic drugs to treat leishmaniasis, such as Amphotericin B, Pentavalent antimony, Miltefosine, but, all of them have limitations because they can induce acute toxicity, teratogenicity effects and drug resistance. Furthermore, many available vaccines that were investigated did not have acceptable results because they did not provide immunogenic protection[48].

Several HDAC proteins have been identified in *Leishmania*: LmJF.21.0680, LmJF.24.1370 are homologous proteins of human class I HDACs; LmjF-08.1090 and LmjF.21.1870 are homologous proteins of class II; LmSIR2RP1, LiSIR2RP1 and Sir2-like are homologous proteins of human class III HDACs[49,50].

The biological function of HDACs class I and II has not been fully defined in *Leishmania*. The class III HDACs haa a role in the parasite survival and regulating of the immune system during infection[50].

The activity of Vorinostat against *Leishmania* genus has been demonstrated; it was able (20 μM) to inhibit 20-35% of *Leishmania* growth[8]. There is no information regarding to the effect of Vorinostat in *in vivo* studies during Leishma-

nia infection in mice or hamsters, so it would be interesting to perform these experiments in the future.

Cryptosporidiasis

Cryptosporidium, an enteric parasite, is the second cause of severe diarrhea and is considered a cause of child mortality worldwide[51]. People who are immunocompromised or severely malnourished have symptoms, which can be severe, prolonged and even life threatening[52]. The main route of transmission is the oral-fecal, either by ingestion of contaminated water or food, or by person-to-person or animal-to-human transmission; the infective form are sporulated oocysts, which enclose four infectious sporozoites and they stick to the host's enterocytes to develop into spherical trophozoites, which then undergo an asexual reproduction and form merozoites, which undergo other processes to end up as oocytes again. Currently, there is not effective treatment available to clear the infection and nitazoxanide is the only drug approved to use against cryptosporidiosis in immunocompetent patients and children older than one year of age. Other available alternatives have been proposed but were not approved for cryptosporidiosis because of their low efficiency[53,54].

In *Cryptosporidium*, a HDAC-like protein has been described; CpHDAC3 which is highly divergent but is inhibited by Vorinostat. CpHDAC3 it has strong ability to regulate DNA transcription during intracellular development of different stages of this parasite[55,56].

In vitro studies have evaluated the anti-cryptosporidial activity of 1200 existing drugs. There were 15 top hits against the growth of *C. parvum*, among them, Vorinostat, it was observed that half maximal effective concentration (EC_{50}) was 0.203 μM[56]. *In vivo* studies performed in a mice model with acute cryptosporidial infection and, treated with Vorinostat at 25 mg/kg per day for 6 days, showed a decrement in the oocysts production[56]. Therefore, this study concluded that Vorinostat might be a useful drug to treat human cryptosporidiosis at a low nanomolar doses.

Amoebiasis

The responsible agent of human amoebiasis is *Entamoeba histolytica*, an anaerobic parasite[57]. People could be affected by this protozoan when they present some risk factors, such as living in endemic areas or tropical regions, poorly sanitized areas; being immigrants or travelers, performing unhygienic sexual practices[57,58]. The infection is established with the ingestion of cysts that convert into trophozoites and colonize the large intestine, which, when added to virulence factors, can lead to several complications. All patients with amoebiasis should be treated; thus, treatment depends on whether the infection is asymptomatic, it may be used only a luminal agent, such as paromomycin; while for invasive amoebiasis and extra intestinal disease, nitroimidazole agents are used (metronidazole, tinidazole) since they are highly effective at eliminating invading trophozoites and must be followed by paromomycin. Nevertheless, they should not be administered at the same time[59]. Some side effects of metronidazole include nausea, headache, anorexia, metallic taste, peripheral neuropathy, and disulfiram-like reaction with alcohol[60,61].

In *Entamoeba histolytica* it has been reported a HDAC protein: *Eh*HDAC a homologous protein of human class I HDACs; its biological functions have not been clearly defined but it is highly probable that it has a similar role to other HDACs, such as transcription of genes that favor protozoan survival[62].

In vitro analysis showed that Vorinostat (2.5, 5 and 7.5 μM) inhibits *E. histolytica* growth. Likewise, according to *in silico* analysis, Vorinostat binds to *Eh*HDAC in the same way they do with human HDAC, due to its high structural homology. Vorinostat binding to *Eh*HDAC could explain the anti-amebic effect[63].

Therefore, to be more certain of Vorinostat's antiparasitic function against *E. histolytica*, it is necessary to perform *in vivo* assays, and, in this way, it could be defined whether it is a drug with potential for the treatment of human amoebiasis.

Schistosomiasis

Schistosomiasis is the endemic parasitosis that can be caused more frequently by *Schistosoma haematobium*, *S. japonicum* or *S. mansoni*; its transmission route is by contaminated water, this parasitic disease is asymptomatic; it can evolve into severe stages until death because there are limitations in the treatment[64]. Praziquantel is a high-spectrum anthelmintic used as the drug of choice in the treatment of all species of schistosomiasis, it is effective against adult schistosome worms, but it has poor activity against immature *Schistosoma* larvae; in these cases, artemisinin derivatives can be used as a complement, nevertheless, its application is limited due to the risk of drug resistance[65,66].

HDAC proteins have been identified in *Schistosoma*: ShHDAC8, SjHDAC8, SmHDAC1, SmHDAC3 and SmHDAC8, respectively to each species, which are homologous proteins of human class I HDACs. HDAC activity is involved in transcriptional activity and apoptosis of *Schistosoma*[50].

In vitro studies on different stages of *S. mansoni* showed that Vorinostat (10 μM) and other HDAC inhibitors had a moderated inhibitory activity against schistosomula and adult worms. Vorinostat showed a lower effectiveness in comparison with other HDAC inhibitors[8]. However, there is little information about *in vivo* studies, so this would be a topic that could be investigated in greater detail to develop a new anti-schistosomiasis therapy.

Conclusions

Drug repositioning is an opportunity area to discover novel antiparasitic drug at low costs and short time, thus, it is necessary to explore new uses of existing drugs. Vorinostat is an effective drug used to treat cutaneous T-cell lymphoma, nevertheless, this drug has showed efficacy *in vitro* and, in some cases, *in vivo*, against parasites that cause parasitic diseases, such as malaria, leishmaniasis, cryptosporidiosis, amoebiasis, and schistosomiasis. The challenge now is to assay its activity in animal models and to evaluate if Vorinostat is safe for humans as new alternative to treat these parasitic infections.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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