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Cannabis sativa: A Source of Antiparasitic Compounds?

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ABSTRACT

Cannabis sativa (hemp, marijuana, ganja) is a plant with industrial, medicinal, and recreational uses that synthesizes phytocannabinoids, a group of compounds from which tetrahydrocannabinol (THC) and cannabidiol (CBD) outstand by their known high and low psychoactive properties. These and other cannabinoids (endocannabinoids and synthetic derivatives with modulating effects over cannabinoid receptors CB1/2) have been tested *in vitro* using cultured parasites and *in vivo* in rodent models of protozoosis affecting the central nervous system as are amoebic encephalopathy, cerebral malaria, brain toxoplasmosis as well as Chagas disease and Leishmaniasis. Helminthiasis mainly includes *Nippotrongyloidosis* and Schistosomiasis and even their effects on ticks as *Boophilus* have been reported. The parasiticidal effect of *C. sativa* extracts and cannabinoids is consistently found although some points of concern arise from animal models because CB1 or CB2 inactivation/inhibition led to distinct outcomes –beneficial or deleterious- in parasite load and host survival, depending on the organism studied. Possible parasitic targets of cannabinoids include arginase, acetylcholinestherase and haemozoin, a product of hemoglobin digestion. Collectively, these data highlight that the potential use of cannabinoids against parasitic infections should consider the effects of these compounds on their known targets at the endocannabinoid system (CB1/2) and the likely target(s) in parasites.

Keywords: Cannabis Sativa; Cannabinoids; Thc; Cbd; Cannabinoid Receptors; Protozoosis; Helminthiasis

Abbreviations: THC: Tetrahydrocannabinol; CBD: Cannabidiol; CBN: Cannabinol; ECS: Endocannabinoid System; ACPA: Arachidonyl-Ciclopropylamide; CNS: Central Nervous System; HEB: Hematoencephalic Barrier; MAGL: Monoacylglycerol Lipase; DAGL: Diacylglycerol Lipase; WGS: Whole Genome Sequencing

Cannabis and Cannabinoids

The genus Cannabis (family *Cannabaceae*) gathers the species *C. sativa, C. indica and C. ruderalis* which are annual male or female plants with unisexual flowers and distinctive digitate leaves and serrate leaflets. *C. sativa* is also recognized as a unique, undivided species [1]. while the term *hemp* is often used to *C. sativa* cultivars grown for industrial or medicinal uses and *marijuana* or *marihuana* are related to cultivars intended for drug preparations associated to medicinal or recreational uses [2]. Indeed, this species has a long and controversial history which origin comes from the Himalayas, spreading to India and Far East (China) since the Neolithic era and to Europe and America at the third-second millennium BC. This plant contains >500 compounds, of which approximately 120 are terpenes and sesquiterpenes (e.g. α-Pinene, Myrcene, Linalool, Limonene, α-Humulene and Caryophyllene), numerous sulfur compounds as Prenythiol (primary odorant) and >110 (phyto)cannabinoids, of which tetrahycrocannabinol (THC), cannabinol (CBN) and cannabidiol (CBD) –also known as ´classical cannabinoids´- outstand due to their abundance and pharmacological activities: THC is the primary psychoactive compound from *C. sativa* [3] and CBD is mildly psychotropic but could block the effects of THC at nervous system [4]. The plant-derived or synthetic THC ([$\triangle^9$-THC, trade name Dronabiol) and other cannabinoids are

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used in treatment of chemotherapy-associated nausea, spasticity and possibly neuropathic pain, epilepsy, glaucoma, multiple sclerosis or feeding disorders [5,6]. otherwise, the isomer $\triangle^8$-THC is under research. Biosynthesis of THC, CBD and its acid precursors THCA, CBDA, CBCA (cannabichromene) and CBGA (cannabigerol) has a common genetic origin and is shown in Figure 1.

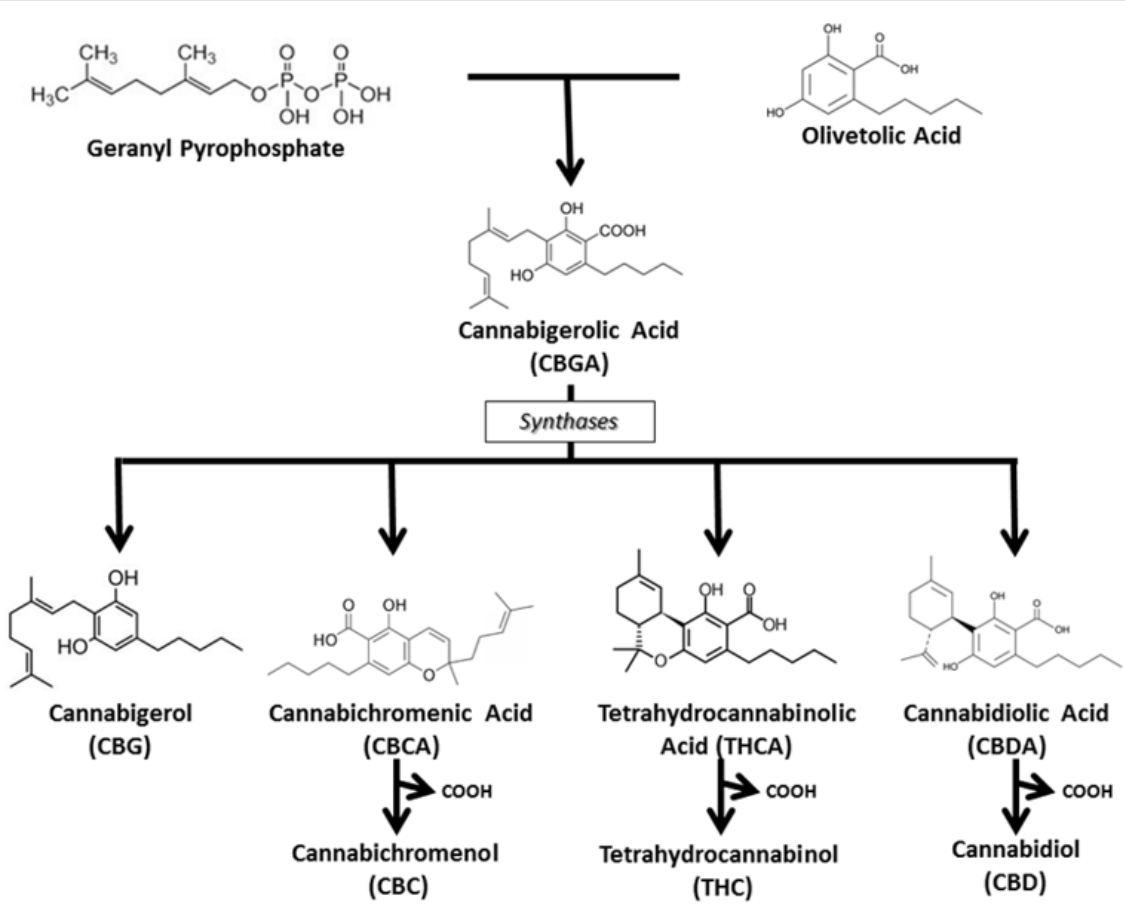

Figure 1: Biosynthesis of cannabinoids in *C. sativa*. In a first step, geranyl pyrophasphate and olivetolic acid are enzymatically combined into CBGA, a common precursor that is independently converted by different FAD-dependent dehydrogenases (synthases) into its base (CBG) and three cannabinoid acids (CBCA, THCA and CBDA). The final 2-decarboxylation step of these acids likely occurs at alkaline conditions, high temperature and low humidity. These cannabinoids are concentrated into a resin within glandular trichomes.

Cannabinoids are classified by their origin or chemical structure. In the first case, there are ´endogenous´ cannabinoids synthesized in humans and other animals (eCBs), ´phytocannabinoids´ (from plants) and ´synthetic´ cannabinoids. In the second classification there are four types: ´classical´ (dibenzopyran derivatives as THC and CBD), ´non-classical´ (pyran ring-lacking bicyclic and tricyclic analogs of THC as CP55940), ´aminoalkylindoles´ (including pravadoline derivatives as WIN55212) and ´eicosanoids´ (arachidonic acid derivatives as anandamide [AEA] and 2-arachidonoylglycerol [2-AG]) and ´eicosanoids´ (e.g., arachidonyl-ciclopropylamide [ACPA) and AM1241) [7]. The endocannabinoid system (ECS) is distributed throughout the body of vertebrates and is composed of specific receptors (CBs), eCBs and enzymes involved in their synthesis and signaling pathways. In humans, it regulates neural functions such as motor coordination, mood, sleep, learning, memory, addictive behavior, pain and immune responses as well (reviewed in [8]). ECS is targeted by cannabinoids through interaction (agonistic or antagonistic) with highly specialized receptors (CB1 and CB2). These G protein-coupled membrane receptors have distinct localizations and functions: CB1 is present in central nervous system (CNS) components as brain (basal ganglia, hippocampus, striatum), cerebellum, reproductive systems and eye, regulating cardiovascular functions and respiration; CB2 is otherwise present in organs (spleen, thymus) and cells (CD4 and CD8 lymphocytes, B lymphocytes, neutrophils, monocytes and NK cells) of the immune system thus playing an important role in immunomodulation [8,9].

Parasites and Cannabinoids

Infection and disease caused by unicellular (protozoa), and multicellular (helminths) parasites is a major health concern worldwide; 17 of these are within WHO´s Neglected Tropical Diseases Initiative from 2006. Protozoosis include Malaria by *Plasmodium falciparum*, African trypanosomiasis by *Trypanosoma gambiense/rhodesiense*, Chagas disease by *T. cruzi*, Leishmaniasis by *Leishmnia sp*., intestinal protozoosis by *Entamoeba histolytica, Giardia duodenalis* and *Cryptosporidium* sp. Within helminthiasis are Schistosomiasis by *S. mansoni/japonicum*, filariasis by *Wuchereria bancroftis, Brugia malayi* and Loa loa, Onchocerciasis by *Onchocerca* volvulus and importantly geohelminthes (*Ascaris lumbricoides, Ancylostoma duodenale/Necator americanus* and *Trichuris trichura*). In 2003 it was estimated that 149 countries are affected by parasites with a burden of 4.4 billion people and 35,000 daily deaths with relatively low financial support for drug development [10]. By the late 1990s and through 2000-2010 human as well parasitic whole genomes have been sequenced, opening the possibility to identify novel drug targets in pathogens. Besides vertebrates, only organisms in the order Chordata –as the ascidian *Ciona intestinalis* and the lancelet *Bramchiostoma floridae*- have been reported to harbor cannabinoid receptors [11,12] and genome-based phylogenetic analyses suggest their absence in microorganisms including virus, proteobacteria, protozoa, nematodes and fungi. Nevertheless, in this ´post-genomic era´ evidence on the effect of *C. sativa* extracts or isolated cannabinoids on protozoan, helminthic and even tick pathogens are emerging.

Protozoa

In Initial *in vitro* studies with the model ciliate *Tetrahymena pyriformis*, △9-THC at 3.2-24 μM showed an inhibitory effect on cell growth, morphology/size, and division in division-synchronized cultures by inhibiting RNA and DNA synthesis [13]. The same cannabinoid along to other 15 derivatives was adverse to growth, enflagellation and encystment –but not motility- of the amoeboflagellate excavate *Naegleria fowleri*, ethiological agent of primary amoebic meningoencephalitis, as well as blocked its cytophatic effects on Vero and HEp-2 cell lines. The antinaeglerial activity was not affected by pyran ring opening, cyclohexyl-to-benzyl ring conversion nor by reverting hydroxyl and pentyl groups on benzene ring and △9-THC was modestly protective to *N.fowleri*-infected mice [14]. The growth of free-living amoeba as *Hartmanella vermiformis*, *Acanthamoeba castellani* –causing granulomatous amebic encephalitis- and *Willaertia magna* was shown affected by eCBs as AEA, 2-AG and 2-O-acyl glycerol (a nonhydrolyzable eCB) at IC_{50}=15-20 μM [15]. Worth of note, these *in vitro* effects on amoebas have not been reflected in models of amoebic infection affecting the CNS. In mice treated with 12 doses of THC (40 mg/kg i.p.) then infected intranasally with *A. culbertsoni* or *A. castellani* displayed an exacerbation of brain infection with increased mortality as compared to untreated mice [16]. This may be explained because treatment with $\triangle^9$-THC caused a lower chemotaxis of macrophages at brain´s sites of infection and decreased expression of proinflammatory cytokines as IL-1α, IL-1β and TNFα in rat microglia [17,18]. in addition to an inhibitory effect of THC on contact-dependent macrophage cytotoxicity [19].

Other protozoa with ability to affect the CNS include *Plasmodium falciparum*, an apicomplexan protozoan causing malaria –the deadliest parasitosis in humans, particularly at sub-Sharan regions-, a fever disease involving multiple parasite stages at blood and liver that eventually may be fatal because the rupture of the hematoencephalic barrier (HEB) promoting brain inflammation and neurological deficits (cerebral malaria). The use of *C. sativa* for treatment of malaria using distinct preparations dates from 5000 years ago. In a murine model of cerebral infection with *P. berghei* ANKA (murine malaria) and treatment with CBD (30 mg/kg for 7 days) and the antimalarial drug artesunate (day 5 p.i.), CBD prevented memory deficits and anxiety behavior after of before parasite clearance leading to a higher survival rate [20]. In a similar model using CB2-knockout mice, these latter also presented higher survival rates as the absence of CB2 expression/function correlated with lower disruption of HEB, lower levels of proinflammatory cytokines (IFNγ and TNFα) and lower parasite load at brain concomitant to lower mononuclear infiltrates and counts of cytotoxic CD8+ T lymphocytes. However, CCL17, a M2 macrophage-derived chemokine, was essential for survival as double knocked mice (CB2-/CCL17-) were susceptible to infection [21]. In an interesting study with the same model where mice were fed *ad libitum* with a preparation of leaves, twigs, and seeds of *C. sativa* (marijuana-type cultivar at 6:3:1 proportion), a slight effect on parasite load but a significantly decrease of symptoms was observed, suggesting that *C. sativa* could produce a tolerance status to malaria with asymptomatic carriage in habitual cannabis consumers [22]. Further studies have identified haemozoin –product of hemoglobin digestion by *P. flaciparum*- as a target of THC (dronabiol) and CBD with THC displaying strong antimalarial activity and CBD presenting mild activity [23]. Toxoplasmosis caused by another apicomplexan, Toxoplasma gondii, is asymptomatic in half of cases but when disease progresses by parasite tropism towards CNS, there may be neuropsychiatric and behavioral disorders, even cryptogenic epilepsy, epileptic seizure and schizophrenia [24]. In infected mice, *T. gondii* disrupts the signaling pathways of ECS at brain as CB1 and monoacylglycerol lipase (MAGL) expression levels are increased but diacylglycerol lipase (DAGL) is unchanged, a process linked to epilepsy [25]. Concurrently, mice with acute or chronic toxoplasmosis displayed lower seizure thresholds while synthetic cannabinoids as JZL184 (MAGL inhibitor), ACEA (CB1 agonist) and AM630 (CB2 antagonist) inhibited the proconvulsant effects of the infection while AM251 (CB1 antagonist) and HU308 (CB2 agonist) intensified proconvulsant effects.

These results highlight a benefit for CB1-MAGL axis stimulation to counteract neurological alterations by parasite load at brain [26].

However, this may also be associated to schizophrenia episodes where levels of AEA, a neuroprotective eCB and CB1 agonist at CNS and CB2 agonist at periphery, are increased three-fold systemically [27]. Other protozoal diseases with high burden are caused by trypanosomatids of the genus *Trypanosoma* and *Leishmania*. Chagas disease (American trypanosomiasis) caused by *T. cruzi* is a major health problem that in chronic stages may cause heart disease (45% cases) along to enlargement of esophagus and colon (21%) and nerve damage (10%) [28]. The use of a synthetic cannabinoid as (+) WIN55,212 produced high reduction in invasion of cardiac myoblasts by the parasite; nevertheless *in vivo* experiments with infected mice showed reduced cardiac inflammation and increased parasitemia without beneficial effect on cardiac parasitosis or survival. These data suggest that cannabinoids could adversely affect cardiac repair mechanisms and homeostasis, raising concerns about their therapeutic utility in chronic infections [29]. In African trypanosomiasis caused by *T. brucei*, experimental therapy assays in rats reported curative effect of *C. sativa* aqueous extracts and two fractions of crude extracts as assessed by elimination of blood trypanosomatids [30]. As Malaria and Trypanosomiasis, Leishmaniasis is a insect vector-borne parasitosis caused by 20 species including *L. donovani* and *L. Mexicana*. This disease causes cutaneous, mucocutaneous and visceral ("kala-azar") presentations and the latter is deadly if untreated. In reports studying plant-feeding habits of sandflies transmitting Leishmaniasis, particularly *Phlebotomus*, these insects have preference for *C. sativa* because, at least, of its high caloric content [31]. This implies that *Leishmania sp.* could be exposed to phytocannabinoids within sandflies and, if tolerance proceeds, these parasites might be more difficult to treat in human hosts with *C. sativa*-derived cannabinoids. Also, recent bioinformatics approaches suggest that arginase, a key enzyme of the polyamine synthesis pathway, is predicted to be inactivated by several cannabinoid and non-cannabinoid compounds from *C. sativa* [32]. Moreover, in a recent work where 24 derivatives of $\triangle^8$-THC, $\triangle^9$-THC and $\triangle^9$-THCA (18 new) were obtained by photooxygenation and tested for binding to CBs. The compounds named as 7 and 21 showed affinities towards CB1 and the compound 23 displayed affinity to CB2 whilst the compound 14 displayed strong *in vitro* activity (IC50 < 1 μg/mL) against *P. falciparum* and *Leishmania sp*. [33].

Helminthes

This parasitic group gathers worms with obvious morphological differences (nematodes, cestodes and trematodes) that infect approximately two billion individuals worldwide. In some populations, cannabis has been used unconsciously by foragers as an anthelmintic [34]. *C. sativa* extracts have shown nematocidal activity on plant pathogens such as *Meloidogyne incognita* [35]. In mice infected with the intestinal nematode *Nippostrongylus brasiliensis* (which has a life cycle like human-pathogenic hookworms), eCBs including AEA and 2-AE were increased at lung and intestine. Inhibition of CB1 with AM6545 promoted an increased worm burden and egg output as well as decreased levels of Th2 cytokine IL-5. Interestingly, transcriptomics analyses coupled to mass spectrometry and qPCR in developmental stages of *N. brasiliensis* revealed that this and other worms can produce their own eCBs, peaking at infectious larval stage. These studies open the possibility that parasitic eCBs (a non-previously described eCB group) could play a role in regulation of host immune responses that might lead to parasite expulsion [36]. In trematodes as *Schistosoma japonicum,* the blood fluke causing periportal fibrosis and liver cirrhosis in Asian populations, studies in mice infected abdominally with cercaria displayed higher expression of CB1 and CB2 and increased AEA serum levels associated to the onset of liver fibrosis [37]. In this pathology, hepatic stellate cells expressed higher levels of CB1 and fibrotic markers with increased NADH oxidase activities (Nox1 and Nox4) upon stimulus with whole parasites or soluble egg antigens, hence involving increased superoxide anion (O2-) production. Silencing CB1 and Nox1 and Nox4 expression bi siRNAs abolished the expression of fibrotic markers, indicating the involvement of CB1, eCBs and oxidative stress in the onset of fibrotic changes at liver [38]. Consistent with these notions, the combined treatment with antifluke compound (Praziquantel) with Rimonabant (SR141716, a CB1 antagonist) inhibited the expression of fibrotic markers and liver fibrosis in infected mice [39].

Ticks

These organisms are arachnids, external parasites within the Ixodida order that live by feeding on the blood of mammalian and bird hosts. Ticks and tick-borne diseases are of major concern in the livestock industry. It is documented that certain tick-derived molecules may interact with cannabinoid receptors (reviewed in [40]). Specific data about the effect of cannabinoids on ticks are scarce. Nonetheless extracts from areal and root parts of *C. sativa* have a significant inhibitory effect on egg laying, egg hatching and total larval mortality at 40 mg/mL against *Riphicephalus (Boophilus) microplus*, an important livestock tick. It was found that a 45% extract applied to larvae-infected cattle reduced tick burden by 96 hrs. post-treatment. By taking acetylcholinesterase (AChE) from R. microplus as likely target, bioinformatics analyses predict that the phytocannabinoid CBD was predicted to be a potent inhibitor (docking score: -14.38) [41]. thereby, profiling this compound to further studies on tick control.

Parasitic Targets of Cannabinoids

As aforementioned, the completion of Whole Genome Sequencing (WGS) projects in protozoa and helminthes allows to perform drug discovery strategies based on pure (endogenous or recombinant) molecules by screening of compounds from commercial sources, *in-house* collections or drug libraries. Likewise new drug targets may be identified with the aid of computational resources such as molecular modeling, docking and molecular dynamics simulations. In the

post-genomic era (from around 2010 to date) activity-based drug screening/discovery, i.e., *in vitro* assays testing the parasiticidal activity of *C. sativa* extracts and cannabinoids, is still the main strategy used. As a result, a few parasitic molecules are currently proposed as cannabinoid targets. In *Leishmania sp.* the key enzyme of the polyamine synthetic pathway, namely arginase, has been proposed from bioinformatics inferences [32]. This enzyme has been crystallized (PDB ID: 4ITY) and by comparative docking with human arginase (PDB ID: 3kv2), both molecules may interact with Δ9-THC displaying similar affinities (-6.02 and -6.35 kCal/mol) as well as with caryophyllene oxide and CBD. At this regard, it should be tested with purified and competent enzymes if phytocannabinoids could have selectivity to the parasitic arginase before further evaluations (Figure 2A). Another likely target of Δ9-THC is hemozoin from *Plasmodium*, which was proposed on the basis of the observed inhibition of the synthetic analog β-haematin [23]. Hemozoin is a crystal complex formed by heme dimers bound by reciprocal iron-carboxylate interactions and stabilized by hydrogen bonding (Figure 2B). However, Δ9-THC did not block hemozoin formation but showed *antimalarial* activity, suggesting that hemozoin synthesis is not targeted by this phytocannabinoid. Therefore, further studies in animal models of malaria deserve to validate these findings. In addition, a likely target of CBD is acetylcholinesterase (choline diesterase) in *R. microplus* tick as inferred from molecular docking studies [41]. Of note, this enzyme is present on the surface of trematodes as *S. japonicum* and *S. mansoni* serving as a protection against overactivation and blocking of acetylcholine receptor and is targeted by anti-schistosomial drugs as metrifonate and oxamniquine whilst phytocannabinoids are well known acetylcholine inhibitors [42] (Figure 2C). These notions reinforce the potential application of phytocannabinoids for control of external parasites.

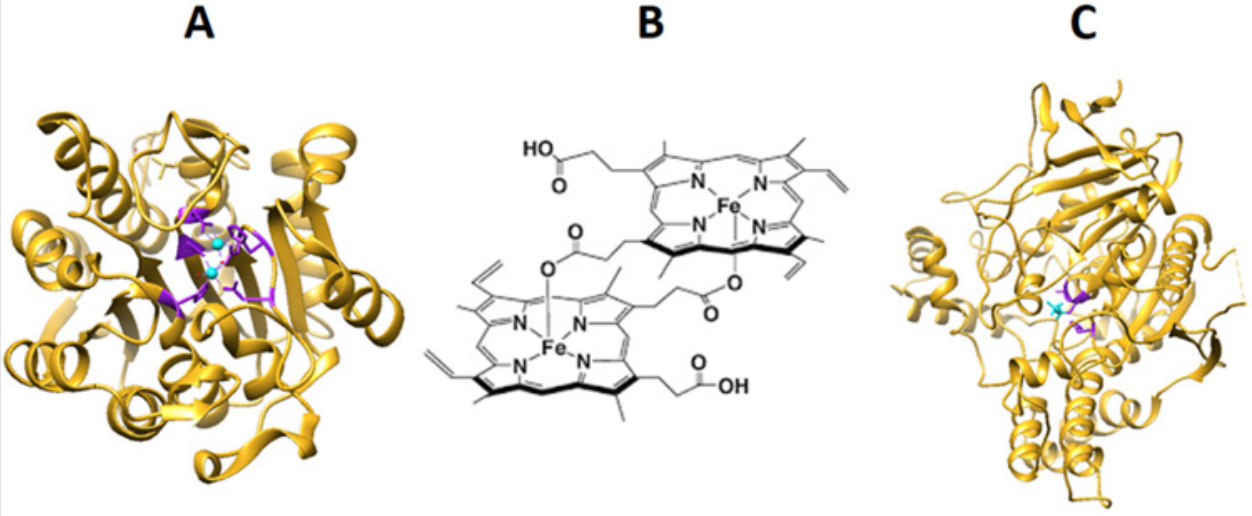

Figure 2: Molecular targets of cannabinoids in parasites.

a) Protein model of arginase from *Leishmania sp.* (PDB ID: 4ITY). Active site residues are displayed in stick conformation and colored purple. Two Mn ions coordinated at the active site are shown as spheres colored in cyan.

b) Haemozoin unit structure as produced by *Plasmodium* from hemoglobin digestion.

c) Protein model of acetylcholinesterase of the tick *R. micro plus* obtained by homology with Torpedo californica enzyme (PDB ID: 2ACE) as template. The substrate acetylcholine is displayed in stick conformation and colored in cyan and the active site residues are colored in purple. Structure models in (A) and (C) were visualized and edited using UCSF Chimera v1.10.

Concluding Remarks

Plant-derived compounds have multiple beneficial activities for human health, including new candidates for the treatment of parasitic diseases. Among these are macrocyclic lactones [43] terpenes [44] and polyphenols [45]. Unlike most plant species, *C. sativa* (hemp, marijuana or ganja) is a rich source of both products of industrial interest and hytomedicinal compounds as well, where phytocannabinoids as THC and CBD –highly and scarcely psychoactive respectively- outstand because of its activity at the ECS, primarily on CB1 and CB2, which underlie their effects on the CNS. At the light of experimental evidence, the potential application of cannabinoids in parasitosis is generally promising on the basis of their parasiticidal *in vitro* activities; however, some concerns and questions raise from *in vivo* data derived from rodent models and insect vectors. Firstly, in some parasitic infections affecting the brain (e.g. *Acantamoeba sp.*), Δ9-THC exacerbates parasitosis instead improving the outcome as consequence of immunosuppressive mechanisms that affect inflammation and macrophage activation. Secondly, data from models of murine malaria treated with marijuana preparations suggest that habitual cannabis consumers

could generate tolerance to parasitosis along to an asymptomatic carrier status, thereby being a potential source of transmission. Thirdly, synthetic cannabinoids as (+) WIN55,212 could be deleterious in chronic Chagas disease as cardiac homeostasis may be compromised and heart failure causes most deaths by *T. cruzi*. Fourthly, phlebotomine vectors of *Leishmania sp.* could generate and spread phytocannabinoid tolerant/ resistant parasites if these sandflies have constant access to feeding with *C. sativa* plants. Fifthly, recent studies indicate that several nematodes produce their own eCBs [36].

It is conceivable that these "parasitic cannabinoids" may help highly prevalent parasites as geohelminthes (*Ascaris, Ancylostoma, Necator, Trichuris*) to cope and eventually suppress host immune responses. Future work addressing these points is warranted. The use of known phytocannabinoids and new (synthetic) cannabinoids in parasitic diseases is a promising field, albeit their effects on elements of the ECS -particularly CB1/2- and over parasite load and survival are not easily predictable. For instance, CB1 activation or CB2 inactivation/inhibition improves parasitic elimination and survival outcome in murine models of malaria and toxoplasmosis [21,26]. However, in mice infected by the nematode *N. brasiliensis*, CB1 inhibition promotes higher worm burden whereas CB1 activation is linked to appearance of fibrotic liver damage in rodents infected with the trematode *S. japonicum* [36,38]. In this still complex scenario, the combination of an antiparasitic drug with a cannabinoid still seems a viable option by the possibility to pursue synergistic effects. This is supported by (a) the hypothetical pharmacokinetic distribution of drugs, where surface-exposed CB1/2 might be more easily reached by circulating cannabinoids as compared to some of the proposed parasitic targets that have intracellular localization (e.g, arginase and haemozoin); and (b) results reported with CBD+artesunate in murine malaria and Praziquanttel+Rimonavant in murine Schistosomiasis [20,39]. In summary, the convenience of activating or inhibiting elements of the ECS towards an effective parasiticidal and anti-parasitosis effect depends on the pathogen being addressed, involving the knowledge of the selectivity of the cannabinoid towards a given element of the ECS and a specific target in the parasite, Therefore, the controversial nature of *Cannabis* also embraces its antiparasitic properties.

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