

Catechins as Emerging and Promising Antiparasitic Agents

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ABSTRACT

Catechins are polyphenols present in green tea and other plant species as a defense against pathogen insults that profile their health-promoting and anti-infectious activities in humans. Worth noting their anti-parasite effects have emerged in recent years. In this review, we focus on the effect of catechins over growth and pathogenic mechanisms of a variety of extracellular, anaerobic (*Giardia*, *Entamoeba*) and intracellular, apicomplexan (*Plasmodium*) and kinetoplastid (*Trypanosoma*, *Leishmania*) protozoa and nematodes of livestock impact as *Teladorsagia*, *Trichostrongylus*, *Ascaris* and *Haemonchus*. Moreover, an inhibitory effect of (galloyl)-catechins on allergenic proteases from mites has been reported. Altogether, these data pinpoint (galloyl)-catechins as candidates for novel alternatives in therapeutic intervention and therapy-associated problems, such as secondary effects and drug resistance in parasitic infections.

Introduction

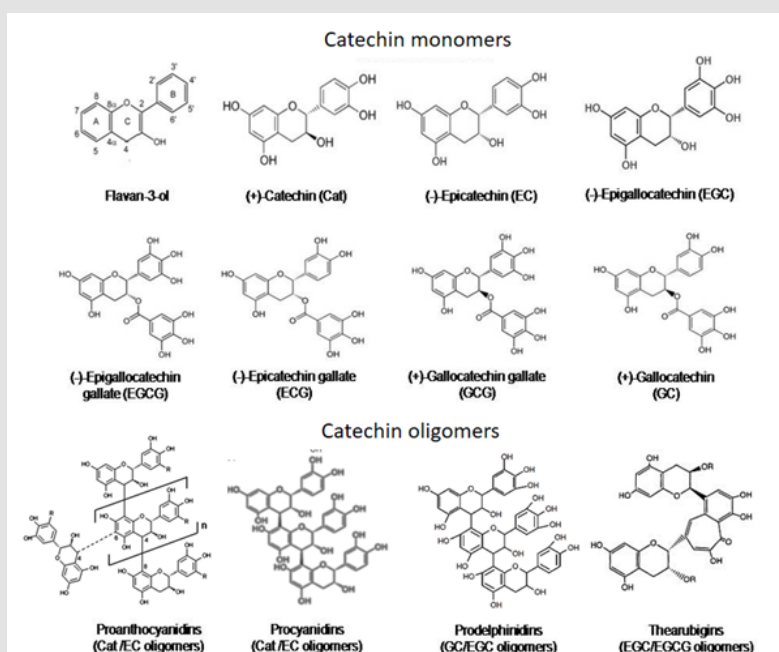


Figure 1: Chemical structures of catechin monomers and oligomers included in this work.

Catechins (from “catechu”, a boiled extract from *Acacia catechu* L.f) are a group of polyphenol compounds from plants classified within the subclass known as flavan-3-ols (flavanols) of the flavonoid family. Flavanols include the precursor isomers (+)-catechin (C) and (-)-epicatechin (EC), as well as, their gallate ester derivatives: (-)-epigallocatechingallate (EGCG), (-)-epicatechingallate (ECG) and (-)-epigallocatechin (EGC) along to their corresponding epimers: (+)-gallocatechingallate (GCG) and (+)-gallocatechin (GC) (Figure 1). Catechins are abundant in extracts derived from the tea plant (*Camellia sinensis*), in cocoa and some chocolates (from *Theobroma cacao* seeds), these are also found in many other plant species and are present in human diet within common foodstuffs, herbal remedies, dairy products, fruits (apple, grape, berries), vegetables and in wine as well [1,2]. Catechins are also found as polymeric condensation complexes. One major class of condensed catechins is the proanthocyanidin group, also called as “condensed tannins”, comprising two main categories based on A-ring substitutions: phloroglucinols and resorcinols. Among these, procyanidins and prodelphinidins are the phloroglucinol-type proanthocyanidins most found in (Figure 1). Otherwise during fermentation of black tea the reddish thearubigins that result from condensation of EGC and EGCG, namely theaflavins, are formed [3] (Figure 1).

Since the past two decades, there has been an increasing interest to consider catechins as an alternative for pharmacological intervention in a spectrum of therapeutic issues as diabetes, neuropathic pain, obesity, neurodegenerative disorders and antimicrobial activities [4-8]. In general, the diverse activities displayed by catechins and condensed tannins are dependent on the catechin type, suggesting a clear influence of the galloyl moiety [9-12]. On the other hand, pathogenic organisms as endoparasites (protozoa and helminthes) and ecto-parasites (e.g. mites) are major but often neglected infectious agents causing severe health problems of high morbidity and/or mortality in clinical and veterinary practice. These are transmitted by multiple routes: waterborne, foodborne, by soil or vectors and have complex life cycles involving, importantly, multiple morphological stages that have limited the establishment of effective vaccines. Also, side effects of and resistance to prescribed drugs are reportedly growing issues that make necessary a continuous search for new and safer antiparasitic compounds [13]. In this context, the recent completion of parasite genome sequencing projects provides a useful platform towards drug target deconvolution along to molecular databases (chemicals, proteins) to decipher the mode of action of parasitocidal agents.

Antiprotozoal Action of Catechins

Protozoa include unicellular eukaryotes that account for 30% of all known parasite species (21 out of 69) causing human disease that usually requires therapeutic intervention [14]. In this scenario, various monomeric catechins have been tested against extracellular, intestinal, and microaerophilic protozoa as

Giardia duodenalis and *Entamoeba histolytica* that have pathogenic (trophozoite) and infectious (cyst) stages and are commonly associated to infectious diarrhea. In studies on inhibition of trophozoite growth *in vitro* using a set of 18 plant flavonoids that included three catechins, (-)-EC and (-)-EGC were the two most potent compounds whilst (+)-Cat had the sixth efficacy against these two *Helianthemum glomeratum* pathogens [15]. Likewise (-)-EC and (+)-Cat were isolated from both *Geranium mexicanum* roots and aerial parts of *Rubus coriifolius* Focke, with the former being the most effective antiamebic and anti-giardial component and the latter displaying moderate activity [16,17]. Other Mexican medicinal plant, *Helianthemum glomeratum* contained both (-)-EGC and (-)-EGCG of which the former was equipotent to (-)-EC and the latter to (+)-Cat against *Giardia* and *Entamoeba* [18]. These results give evidence on the importance of the presence of 3-OH group (as *minus* isomer hence in *cis*-configuration with B-ring) for higher antiamebic and anti-giardial activities of catechin monomers. In addition the precursor (+)-Cat and the derivative catechin-3-O- α -L-rhamnopyranoside isolated from the dioecious hemiparasite shrub *Osyris alba* displayed a toxicity almost 20-fold lower (i.e. higher IC₅₀ values) against cancer (Hep-2) and non-malignant (Vero) cells than against *Giardia* and *Entamoeba*.

Metronidazole, a current drug of choice against these parasites but with emerging evidence of drug-resistance [19] and variable drug susceptibility [20] exhibited a toxicity index better by far (above 200-fold); however catechins have still a promisingly favorable profile for further preclinical tests [21]. Consistent to this notion, (-)-EC had a better efficacy (i.e. lower ED₅₀ values) in CD-1 mice experimentally infected with *G. duodenalis* than metronidazole and other flavonoids as kaempferol and tiliroside isolated from the Mexican medicinal plants *G. mexicanum*, *Cuphea pinetorum*, *H. glomeratum* and *R. coriifolius* [22]. The mechanism of catechin-induced cell death in these two protozoa harbouring mitochondria instead typical mitochondria has not been elucidated but *Entamoeba* trophozoites exposed to (-)-EC displayed chromatin clumping, increased glycogen deposits, reduced number and size of cytoplasmic vacuoles and alteration of cytoskeletal functions [23,24]. These features resemble programmed cell death (PCD)-like induced by protein translation inhibitors and nitrosative stress-inducing agents in this organism.

Regarding oligomeric catechins, in roots of the plant *Geranium niveum* two uncommon A-type proanthocyanidins, named as Geranins A and B [epiafzelechin-(4 β -8,2 β -O-7)-afzelechin and epi-catechin-(4 β -8,2 β -O-7)-afzelechin respectively] were initially isolated and showed inhibitory effect on the growth of both parasites albeit *Giardia* was highly susceptible to both compounds and Geranin A had a much lower efficacy on *E. histolytica* trophozoites [25]. Further isolation of Geranins C and D [epi-afzelechin-(4 β -8,2 β -O-7)-gallocatechin and epi-afzelechin-(4 β -8,2 β -O-7)-afzelechin-(4 β -8,2 β -O-7)-afzelechin respectively] rendered a moderate activity for the Geranin D against both parasites while

Geranin C was moderately active only against *E. histolytica* [26]. Thus, the efficacy order for Geranins was A>B>D>C for *Giardia* and B>D>C>A for *Entamoeba*.

Other group of protozoa is the kinetoplastids causing Chagas disease (*T. cruzi*) and the cutaneous/mucocutaneous/visceral leishmaniasis complex (e.g. *Leishmania major*, *L. amazonensis* and *L. donovani* respectively). In Chagas disease and Leishmaniasis, these organisms have the intracellular amastigote stage within macrophages or tissue cells and extracellular trypomastigote/epimastigote (*T. cruzi*) or promastigote (*Leishmania*, of which the Trypanosomatid group exclusively clusters parasitic organisms causing important human diseases as sleeping sickness (e.g. *Trypanosoma brucei*) stages. Noteworthy the characteristic kinetoplast is a DNA-rich region within a single large mitochondrion that differs both structurally and functionally from mammalian ones hence renders it an attractive chemotherapeutic target [27]. In this sense the green tea's most abundant catechin, EGCG, decreased viability of intracellular *Leishmania* without significant induction of nitric oxide production by infected macrophages [28] and caused structural and functional collapse of mitochondria in *L. amazonensis* promastigotes associated to reduced parasite burden in infected mice [29,30]. Also, ROS-mediated oxidative stress caused by EGCG was proposed as parasitocidal mechanism in *L. braziliensis* promastigotes and amastigotes [31]. Recent studies denoted the importance of the galloyl group for activity against *L. infantum* promastigotes because the efficacy of derivatives was EGCG>ECG>Cat [32]. In *Trypanosoma cruzi*, from a set of 8 (galloyl)-catechins from *C. sinensis*, GCG and EGCG were the most potent compounds with IC₅₀ values in the picomolar range against bloodstream trypomastigotes and in the micromolar range against amastigotes infecting Vero cells [33]. Further, intraperitoneal administration of EGCG in a murine model of acute Chagas disease increased survival from 11 to 60% and diminished parasitemia by 50%; interestingly this compound induced PCD-like in epimastigotes as assessed by DNA oligosomal fragmentation [34].

Within the protozoal phylum apicomplexa (i.e. alveolate intracellular organisms that use a cytoskeleton-rich apical complex to penetrate host cells), *Plasmodium* is a prominent genus infecting a broad range of vertebrates including reptiles, birds, and mammals. In human beings *P. falciparum* is the deadliest species as it causes malaria and presents several stages within mosquito vector and at liver and red cells in vertebrate hosts. Other important apicomplexan genus is *Babesia* that infects livestock worldwide, penetrates erythrocytes and is transmitted by ticks. In southern multimammate rodents (*Mastomys coucha*) infected with *P. berghei*, treatment with (+)-Cat reduced parasitemia and erythrocytic oxidative stress while improving host survival [35]. Remarkably EGCG displays effects in *P. falciparum* at several levels: in a structure-based drug screening using the crystal structure of the human intercellular adhesion molecule (ICAM-1), EGCG was shown

to block the binding of *P. falciparum*-infected erythrocytes to ICAM-1 that is exposed on endothelial cell surface, an event associated to pathology in malaria [36]. Moreover, this inhibition varied amongst parasite isolates in the range 37-80% at 50µM EGCG, which was suggested to mimic the L43 loop of ICAM-1 [37]. Also, the membrane permeabilizer digitonin synergized the cytotoxicity of EGCG against liver sporozoites and additively inhibited parasite motility [38]. Furthermore, EGCG exhibits disaggregating effect on amyloid-like fibrils formed by the vaccine candidate merozoite surface protein-2 (MSP-2) causing oligomer release [39]. In addition, EGCG was shown able to interact with the chaperone HSP70 of *P. falciparum* interfering with its ATPase and chaperone functions [40]. In the case of bovine *B. bovis* and murine *B. microti*, EGCG displays an adverse effect on parasite growth *in vitro* (IC₅₀ in the micromolar range) and at 5-10mg/kg it cleared parasites in infected mice [41].

Anthelmintic Activity of Catechins

Parasitic helminthes include the phyla Nematoda (roundworms) and Platyhelminthes (flatworms) [42]. Soil-transmitted helminthes are the most common infectious agents of humans in developing countries, mainly at tropical and subtropical areas as sub-Saharan Africa, America, China, and oriental Asia region [43]. Helminthiasis is a global public health problem. Approximately, 15 million of people are infected by soil-transmitted helminthes, which represent a quarter of world's population [44]. The infections occur when the humans ingest infecting eggs (*Ascaris lumbricoides* and *Trichuris trichiura*) or larvae (*Ancylostoma duodenale*) in contaminated food, or through penetration of the skin by infective hookworm larvae in soil (*Necator americanus* and *Ancylostoma duodenale*) [45] King) affecting over 1 billion persons worldwide. Their prevalence is closely linked to the presence of severe poverty and its associated sub-standard housing and sanitation. The last decade has seen a remarkable increase in our understanding of the true disease burden of helminth infections, and there has been increasing momentum on the part of national and non-governmental developmental organizations for prevention and control of these diseases. The expansion in mass treatment programmes for their control has yielded some significant successes. However, challenges remain in terms of ecological heterogeneity in transmission, incomplete drug uptake, and the likelihood of emerging drug resistance. The development of new, more-sensitive diagnostics is now broadening our knowledge of infection prevalence and of the risk of reinfection and has enhanced our knowledge of the prevalence of concurrent helminth infections. Adoption of these new diagnostic techniques for large-scale screening and surveillance will require adaptation of current mass treatment guidelines for control as programmes move from initial morbidity control objectives toward coordinated interventions aimed at local elimination."author": [{"dropping-particle": "", "family": "King", "given": "Charles H", "non-dropping-particle": "", "parse-names": false, "suffix": ""}], "container-title": "Advances in parasitology", "id": "ITEM-1", "issued": {"date-par

ts":{"2019"}], "language": "eng", "page": "11-30", "publisher-place": "England", "title": "Helminthiasis Epidemiology and Control: Scoring Successes and Meeting the Remaining Challenges.", "type": "article-journal", "volume": "103", "uris": ["http://www.mendeley.com/documents/?uuid=b034daec-8568-4046-addc-1003762f34cc"], "mendeley": {"formattedCitation": "[42]", "manualFormatting": "King, 2019. Current clinical trials efforts mainly focus in mass drug administration (MDA) strategies as the best way for control of soil-transmitted helminthes (STH), addressing the school-age child sector and adults with high risk-infection occupations [46]. However, despite to the wide options of anti-helminthic drugs available (albendazole, mebendazole, benzimidazole, Praziquantel, oxamniquine, ivermectin and others), helminthiasis continue to grow worldwide and, in a similar form, drug-resistance nematodes increase with particular emphasis on livestock [45].

In this regard, this review analyzes the catechins as potential anthelmintic compounds. Evidence indicates that Cat has effects on motility and mortality of helminthes, prompting catechins as promising natural antiparasitic agents. In line with this, investigations support the EC properties against the trematode *Paramphistomum cervi* [47]. Moreover, EC was related to anti-cestode activity against *Raillietina echinobothrida*, suggesting a mechanism of action associated to decreased nitric oxide synthase (NOS) and the subsequent nitric oxide (NO) production [48]. Besides, *in vitro* studies support that compounds CG, ECG, GC, EGC, and EGCG, isolated from *Acacia nilotica* fruits, have nematocidal activity against *Onchocerca ochengi* and the model *Caenorhabditis elegans*, remarking the anthelmintic actions of catechins [49]. On the other hand, the activity and migration of helminthes larvae, as *Ascaris suum*, is inhibited by action of GC, EGC and EGCG compounds [50,51]. In a similar form, polyphenols including catechins, have an important role in a very early stage of host invasion parasitic, which explains the inhibitory effects on gastro-intestinal infection of some nematodes [52]. Moreover, the inhibitory effects of CG, EGC, GCG and EGCG were observed on egg hatching and larvae development (L3) of *Trichostrongylus colubriformis* [53]. In a short summary, there are significant evidence about of potential use of catechins against experimental helminthiasis, notwithstanding, clinical trials that support the anti-helminthic effect of catechins have not been developed yet.

Catechins and Mites

Mites are small arthropods that along to ticks are contained in the arachnid taxon Acari; some of these are parasites, causing diseases such as scabies and skin allergies in humans and plant pathologies. In plants as *Quercus ilex* that form erinea (hyperplasic leaf trichomes), these structures are enriched in (-)-Cat and proanthocyanidin B3 for protection upon attack by the mite *Aceria ilicis* [54]. By other side, *Dermatophagoides farinae* is present in-house dust and produces a serine protease (Df-protease) that induces allergy through the kallikrein-kinin system thereby

inducing vascular permeability, inflammation hence allergy in human skin. Catechins inhibited Df-protease-induced kinin release in human plasma in the order EGCG>ECG>EGC>EC and EGCG effectively suppressed vascular permeability in guinea pigs, reinforcing the importance of the galloyl moiety for interaction with this enzyme [55]. In a clinical sense, patients with persistent allergic rhinitis induced by dust mite displayed alleviated symptoms upon treatment with apple polyphenols containing 52% procyanidins and 9% catechins [56].

Catechin Targets in Parasites

Catechins may interact with different kinds of protein molecules or their biological partners that protozoa, helminthes and mites possess; here, the advent and use of newest molecular and bioinformatics tools is encouraging this field. In protozoa as *Plasmodium*, (+)-EGCG can interact with the DE loop of ICAM-1 thereby blocking the cytoadherence of *Plasmodium*-infected erythrocytes to vascular endothelium [36]. Also, surface plasmon resonance assays show that (+)-EGCG inhibits ATPase and chaperone activities of two heat shock proteins at cytosol of *P. falciparum* (HSP70-1 and HSP70-z) [40]. Other studies have shown that catechins target and inhibit enzymes of energy metabolism such as recombinant rat arginase-1 and its *L. amazonensis* homolog (ARG-L) but these are more actives against the parasite enzyme. Interestingly the galloyl moiety adversely affected the interactions with ARG-L thus their effectiveness was (+)-Cat>(-)-EC>(-)-EGCG [57] and the inverse relation was obtained by *in vitro* promastigote viability and *in silico* molecular docking with the redox enzyme trypanothione synthase [32]. For *T.brucei* that relies on fatty acid synthesis for proliferation and virulence, the first enzyme of this pathway, acetyl CoA carboxylase, is phosphorylated then inhibited by activation of AMP-dependent protein kinase which is directly activated by (-)-EGCG in bloodstream and procyclic forms [58].

In helminthes and mites the identification of catechins targets is still limited. Helminthes are gifted with proteins of redox metabolism that have been found targeted by condensed tannins. A nematode-specific, mitochondrial thioredoxin reductase (TrxR) from *H. contortus* is inhibited by theaflavins in a qualitatively similar mode to other known TrxR inhibitors as curcumin and auranofin among others [59]. Likewise, recombinant glutathione S-transferase (GST) from *Ascaris* and *Onchocerca* are inhibited by extracts containing proanthocyanidins from Nigerian traditional plants used against gastrointestinal helminthes [60]. The unique mite target identified so far is the Df-protease that was shown inhibited by EGCG over other less galloylated catechins [55].

Figure 2 depicts the structural alignment of representative targets of catechins, particularly EGCG, in protozoa (*P. falciparum* erythrocyte membrane protein 1), helminthes (*H. contortus* thioredoxin reductase) and mites (Df-protease) with their respective closest homologs (internalin K from *Listeria*

monocytogenes, 82.8% structure homology; mouse mitochondrial TrxR, 92.5% structure homology; human hepsin, 80.4% structure homology). In general, the parasite molecules display substantial structure differences involving moieties with potential docking or targeting by catechins even when compared to host proteins, in a similar way than that reported for other known catechin targets

as are leishmanial arginases and trypanothion synthase. Taken together, these analyses unveil a broad perspective for rational drug design and testing of catechins against parasite molecules that could in turn serve as platform for future therapeutic interventions in the diseases these pathogens cause.

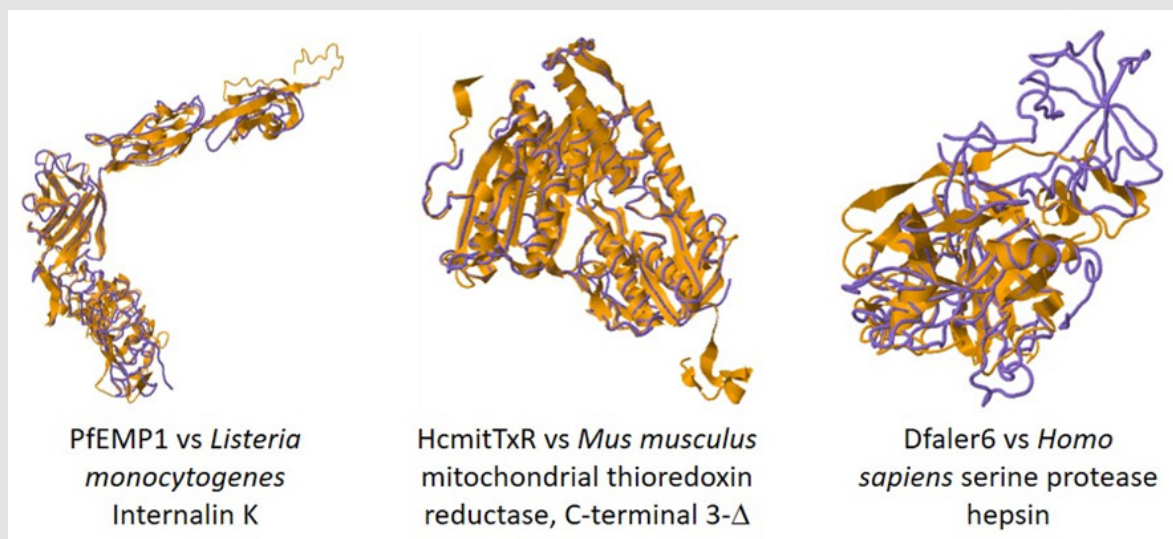


Figure 2: Protein structure alignment of representative catechin targets in protozoa (PfEMP1), helminthes (HcmiTxB) and mites (Dfaler6) (colored in orange) with their closest crystal homologs (Internalin K PDB ID: 4I3aA; MmTrxR PDB ID: 3dggA; HsHepsin PDB ID: 1z8gA) (colored in purple).

Conclusion

Catechins have activity against pathogens from the plants these are synthesized and towards infectious agents affecting humans and companion and livestock animals as well. Their antiparasitic activities have been studied at deeper detail from the past two decades. Monomeric catechins, particularly EGCG, exhibit a broad range of antiprotozoal activity targeting important enzymes of redox and energy metabolism with a favored selectivity in relation with host analogs. Structure-activity relationships mostly show an increased effect by the galloyl moieties of these flavan-3-ols. Condensed tannins, i.e. oligomeric catechins, have cytotoxic effects not only for protozoal but also for helminth pathogens, causing impaired motility, larval ex sheath ment and migration of ruminant and bovine nematodes. In mites, the search for allergen counteraction with catechins is a scarcely explored but very promising issue. In the current absence of proven vaccines against parasites, recent tools as ligand- and target-structure based strategies coupled to formulations with new adjuvants and vehicles will help the future development and exploitation of these important flavonoids in the control of parasitic diseases.

Conflicts of Interest

Authors declare that there are not conflicts of interest concerning this work.

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