Curcuma as a Parasiticidal Agent: A Review

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Abstract
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Members of the *Curcuma* plant species (Zingiberaceae) have been used for centuries in cooking, cosmetics, staining and in traditional medicine as "omnipotent" remedies. Herbal preparations made with, and molecules extracted from, *Curcuma* have been shown to possess a wide variety of pharmacological properties against malignant proliferation, hormonal disorders, inflammation, and parasitosis among other conditions. This review evaluates *Curcuma* and its associated bioactive compounds, particularly focusing on studies examining the parasiticidal activity of these components against the tropical parasites *Plasmodium, Leishmania, Trypanosoma, Schistosoma* and more generally against other cosmopolitan parasites (nematodes, *Babesia, Candida, Giardia, Coccidia* and *Sarcoptes*).

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Introduction
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The *Curcuma* species (Zingiberaceae) are a family of herbaceous perennial plants, widely distributed throughout Asia, where their rhizomes are extensively used in culinary and traditional medicinal practices [1]. Their therapeutic properties have been attributed to the polyphenolic curcuminoid compounds. The most abundant curcuminoid in the rhizome is 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-hepadiene-3,5-dione, commonly known as curcumin (**1**) [2]. Its structure, elucidated at the beginning of the 20th century, includes two oxy-substituted aryl moieties (polyphenols) linked together by two α,β-unsaturated carbonyl groups. The molecule exhibits keto-enol tautomerism (○ **Fig. 1**).

The enol form is stable at high temperatures and in acids, but unstable in alkaline media and under light conditions. Being hydrophobic in nature, the poor solubility of curcumin in aqueous solutions and its instability under physiological conditions, especially in the gut region, lead to a poor oral bioavailability [3]. Rapid metabolism and a high rate of systemic elimination result in low plasma and tissue levels of curcumin. In order to maximize the potential clinical applications of this compound, efforts have been made to circumvent these restrictive pharmacokinetic characteristics [4,5]. Furthermore, the use of this class of molecule as parasiticidal agents has been extensively studied (see [6–8] for reviews).

Around the world, parasites plague human beings, affecting developing countries in particular. In tropical regions, regardless of economic status, plant preparations have been used to cure parasitic disease throughout the ages. *Curcuma* is one of the most commonly used plant genera for this purpose. Our intention is to present a novel review focusing on the antiparasitic effects of *Curcuma*-derived compounds, including curcuminoids and synthetic derivatives, particularly in cases of tropical parasitosis, commonly found in areas where *Curcuma* grows. Furthermore, as infections caused by cosmopolitan parasites are becoming increasingly detrimental to public health in these regions, the effect of *Curcuma* on these parasites will also be reviewed here.

Tropical Parasitosis
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Malaria

Malaria is caused by protozoa of the genus *Plasmodium*, transmitted through the bite of mosquitoes of the *Anopheles* genus. It is considered to be the top parasite affecting human health, killing about 1 million people annually and affecting almost 250 million people around the world [9]. Commonly, affected patients present with fever,
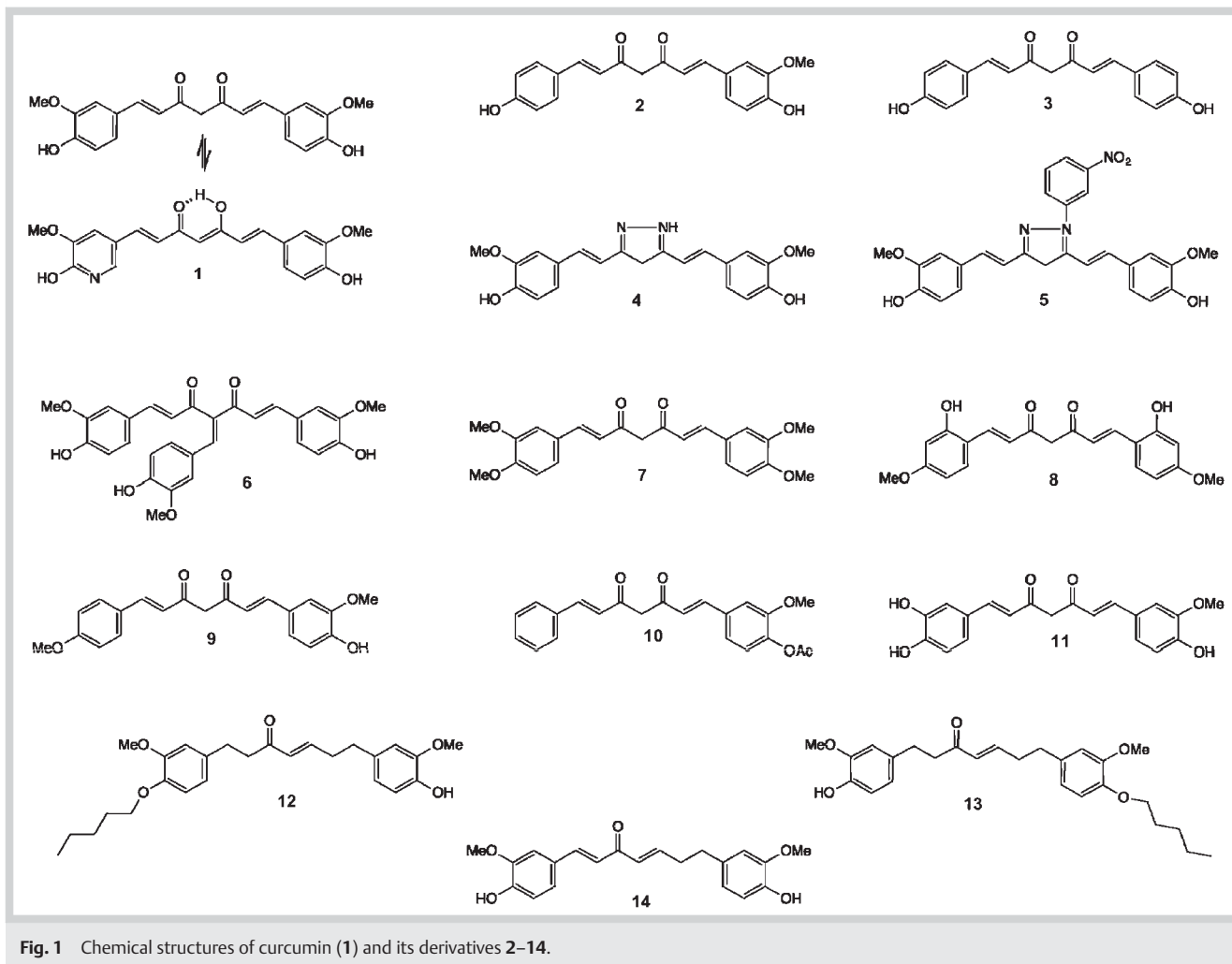
Fig. 1 Chemical structures of curcumin (**1**) and its derivatives **2–14**.

headache, and vomiting about 10 to 15 days after being bitten. Untreated, some species of *Plasmodium* can become life-threatening due to a decrease in the blood supply to vital organs. *Plasmodium* has developed resistance to most antimalarials worldwide. Among the 15 commercially available antimalarials, 12 are derivatives of two natural compounds, quinine and artemisinin, which are still extracted from plants that have been used for centuries in the treatment of intermittent fevers.

Various studies have been undertaken in order to evaluate the antiplasmodial properties of the *Curcuma* extracts, curcumin and its derivatives. Murnigsih et al. [10] showed that water extracts of rhizomes of *C. xanthorrhiza* Roxb. and *C. aeruginosa* Roxb. were able to inhibit 40% and approximately 90%, respectively, of the growth of *P. falciparum in vitro*, but the dose used in their test (1 mg/mL) was relatively high. Rasmussen et al. [11] isolated curcumin (**1**), demethoxycurcumin (**2**) and bis-demethoxycurcumin (**3**), from the rhizomes of *C. longa*. These molecules inhibited 50% of parasite growth *in vitro* at 3–4.2 μg/mL (approximately 8 μM) concentrations, almost 300 times higher than that required of the control drug, chloroquine. Mishra et al. [12] synthesized some curcumin derivatives and claimed that curcumin-pyrazole (**4**), *N*-(3-nitrophenylpyrazole)curcumin (**5**), and 4-(4-hydroxy-3-methoxybenzylidene)curcumin (**6**) were able to inhibit 50% of *P. falciparum* growth in culture more potently than curcumin, at concentrations of less than 1 μM. Bent-

zen et al. [13] and Foller et al. [14] suggested that curcumin promotes erythrocyte cell death by enhancing cytosolic Ca^{2+} activity and ceramide formation, thus leading to red cell membrane structural alterations, which trigger phagocytosis by macrophages. Interestingly, as this phenomenon is not encoded by plasmodial protein machinery, it is thus not expected to generate resistance by genetic mutation of the parasite. Ligeret et al. observed that fluorinated curcumin derivatives, such as atovaquone [15], were able to affect the mitochondrial machinery of *Plasmodium* at concentrations of 5 μM [16], a concentration corresponding to the half maximal inhibition concentration (IC_{50}) of curcumin against erythrocytic stages [17]. Reddy et al. [17] showed that curcumin had an IC_{50} of 5 μM against *P. falciparum in vitro* corroborating the results of Rasmussen et al. [11]. Interestingly they also showed that when administered orally, at a concentration of 100 mg/kg/5 days, it decreased the blood parasitemia of *P. berghei*-infected mice by 80–90%. In the hands of Cui et al. [18], curcumin had an IC_{50} ranging from 20 to 30 μM against *P. falciparum* [both chloroquine-resistant (CQ-R) and -sensitive (CQ-S) strains]. They also showed that curcumin increased the production of reactive oxygen species and inhibited the activity of plasmodial histone acetyltransferase, an enzyme required for chromatin remodeling and transcriptional activation. Singh and Mishra confirmed this observation using bioinformatic techniques [19]. Furthermore, their findings showed that *in silico*,

curcumin could bind to the active site of sarco-endoplasmic reticulum Ca^{2+} ATPase, an ATP coupled Ca^{2+} ion pump involved in metabolic arrest. Based on computational analysis, Ji and Shen also suggested that curcumin could bind to the plasmodium Ca^{2+} ATPase, PfATP6, through hydrophobic interactions and hydrogen bonds and efficiently inhibit this crucial plasmodial enzyme [20]. This finding supports the reported enhancement of antimalarial activity on combining artemisinin with curcumin [21], which forms covalent adducts with the transmembrane proteins. Nandakumar et al. also showed that curcumin and artemisinin were additive *in vitro* and that 3 oral doses (100 mg/kg each) of curcumin after a single administration of the artemisinin derivative arteether (1.5 mg/mouse/IM) were sufficient to cure *P. berghei*-infected mice, preventing further infection outbreaks [21]. However, Martinelli et al. [22] showed that, in combination with a subcurative dose of artemisinin (150 mg/kg/4 days), curcumin at 300 mg/kg/4 days was not able to affect the growth of *P. chabaudi in vivo*, a strain of murine *Plasmodium*, resistant to artemisinin. They also showed that, in combination with piperine (20 mg/kg/ 4 days), which is thought to increase curcumin bioavailability, curcumin alone, or the combination of curcumin and artemisinin had no conclusive effect on the course of plasmodial growth. To increase the bioavailability of both curcumin and artemisin, Lapenna et al. proposed, the use of micelles of sodium dodecyl sulfate (SDS) [5] but this theory remains untested against parasites. Mishra et al. showed synergism between *Andrographis paniculata* (Burm. f.) Nees and *Hedyotis corymbosa* (L.) Lam. methanolic extracts and curcumin against CQ-S and CQ-R strains of *P. falciparum in vitro* [23]. This was also observed *in vivo* against *P. berghei* murine malaria, by administrating mice every day with 7 mg/kg intraperitoneally, until they died at day 13 for the control group, and day 22 for mice treated with the most effective combination, *A. paniculata* and curcumin. Drug combination therapies are now routinely used in endemic areas in an effort to combat antimalarial resistance. One of the most studied mechanisms of chemo-resistance involves a membrane-associated "drug pump" which transports drugs out of the cell against a concentration gradient. One of these, the P-glycoprotein (P-gp) pump, plays a key role in anticancer drug resistance. Interestingly, this protein is also found in *Plasmodium* with a correlation between amplification of its expression and increased resistance to antimalarials (see [24] for a review). Chearwae et al. showed that curcuminoids were able to increase the sensitivity of cancer cells to etoposide by modulating the function of P-gp [25]. Consequently, we can speculate that curcumin derivatives may also act on plasmodial P-gp and could be used in conjunction with antimalarials in areas where resistance prevents their use; however, further experimental research is required to support this theory.

Leishmaniasis

Leishmaniasis is a parasitic disease, caused by a protozoan of the genus *Leishmania*, and transmitted by phlebotomine sandflies. More than 350 million people live in "at risk" areas and more than 12 million people are currently infected [26]. Clinically, cutaneous forms affect the skin and mucus membranes while visceral leishmaniasis affects some internal organs, leading to potentially fatal complications. Few effective drugs are available. Antimony-containing compounds, meglumine antimonate and sodium stibogluconate are generally used as an initial treatment, followed by amphotericin B, fluconazole and pentamidine if necessary. All of these drugs require parenteral administration in equipped health centers. Miltefosine is the only agent that has been shown to be effective by oral administration, but only against some forms of leishmaniasis. Thus alternative treatments are urgently needed.

Koide et al. [27] showed that curcumin inhibited 50% of *L. major* promastigote growth at 37.6 μM. Araujo et al. [28] had similar results with curcumin (IC_{50} of 24 μM) on promastigotes of *L. amazonensis* and also showed that methylcurcumin (**7**) was more active at lower concentrations (< 5 μg/mL). Methylcurcumin administered to Balb/c mice (20 mg/kg) at the time of infection, resulted in a decrease in lesion size of approximately 65%, when measured 75 days after infection. Interestingly, no inflammation was observed in the area where the drug was injected, which may be due to the well-known anti-inflammatory properties of curcuminoids [28].

Rasmussen et al. [11] showed that curcumin (**1**), demethoxycurcumin (**2**) and bis-demethoxycurcumin (**3**), isolated from the rhizomes of *C. longa*, have some parasiticidal activities against *L. major* (IC_{50} ranging from 22 to 60 μM). Curcumin proved to be the most potent of the compounds. Gomes et al. [29] synthesized curcuminoids by condensing 2,4-pentanedione with differently substituted benzaldehydes and found that 1,7-bis-(2-hydroxy-4-methoxyphenyl)-1,6-heptadiene-3,5-dione (**8**) was the most effective against *L. amazonensis* promastigotes (IC_{50} 24 μM).

Saleheen et al. determined the activity of curcumin against promastigote forms of *L. major, L. tropica* and *L. infantum* and showed that it had an average IC_{50} of 5.3 μM [30]. Furthermore, against axenic amastigote cells of the *L. major* strain, curcumin was a more potent parasiticidal agent than pentamidine, the control drug (10 and 13.5 μM, respectively). Alves et al. studied the impact of the synthetic curcuminoids, diarylheptanoids and diarylpentanoids on the growth of promastigotes of *L. amazonensis, L. braziliensis* and *L. chagasi* and against *L. amazonensis* axenic amastigotes. The tested compounds were shown to be most effective against *L. braziliensis* promastigotes (IC_{50} ranged from 2 to 78 μM) [31]. For *L. amazonensis* the IC_{50} values ranged from 1 to 373 μM and 6 to 331 μM for *L. chagasi* promastigotes. In the case of *L. amazonensis axenic* amastigotes, the IC_{50} varied from 56 to 435 μM. Pentamidine isethionate, the reference drug, was as effective as the most potent compound. The authors highlighted that lipophilic diarylheptanoids were more efficient than diarylpentanoids, against the three species of *Leishmania*. Oxygenated functions in the aromatic ring governed the potency of the most active compounds. Finally, *p*-methoxy substituents were also shown to be important for leishmanicidal activity. The authors reported that 5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-4-methoxyphenyl)-1,4,6-heptatrien-3-one (**9**), which contained an *m*-hydroxy moiety in the aromatic ring, was the most active compound against *L. amazonensis* promastigote growth. The curcumin derivative which proved most effective against *L. braziliensis* (IC_{50} of 2 μM), had a *p*-methoxy substituent and a *m*-phenolic group protected by an acetylated function [5-hydroxy-7-(4-acetoxy-3-methoxyphenyl)-1-phenyl-1,4,6-heptatrien-3-one] (**10**) [32]. Das et al. studied the impact of curcumin on *L. donovani,* responsible for visceral forms of the disease and showed that it induced cell cycle arrest at the G2/M phase in promastigote forms [33]. They observed that phosphatidylserines were exposed to the outer leaflet of the plasma membrane and that mitochondrial membrane depolarization followed the elevation of cytosolic calcium concentration. Furthermore, they observed the release of cytochrome *c* into the cytosol and nuclear alterations.

Changtam et al. showed that some curcuminoids (**11**–**14**) exhibited EC_{50} values of less than 5 mM against *L. major* promastigotes and *L. mexicana* amastigotes [34]. On the contrary, Chan et al. showed that the anti-nitric oxide properties of curcumin protected promastigotes and amastigotes of the visceral species, *L. donovani*, and promastigotes of the cutaneous species, *L. major*, against the effects of pro-oxidant molecules *S*-nitroso-*N*-acetyl-D,L-penicillamine and DETANONOate [35]. Most of the published results on curcuminoids against *Leishmania* have been obtained against the promastigote, instead of the more relevant amastigote stage inside macrophages. Consequently it is not clear if the activity described in the literature reflects the real leishmanicidal properties of these molecules. Therefore, the potency of these molecules should perhaps be re-examined in a more appropriate model, such as infected macrophages.

Trypanosomiasis

Trypanosoma are flagellate protozoa belonging to the genus of kinetoplastids. They are transmitted by blood-feeding invertebrates, infecting a variety of hosts and causing various diseases in humans, including Chagas disease (*T. cruzi*) [36] in Central and South America and sleeping sickness (*T. brucei*) in Africa [37]. In mammals they circulate through the blood and tissue fluids and may also be localized intracellularly (*T. cruzi*). Treatments are limited to benznidazol and nifurtimox for Chagas disease with low curative rates if administrated in the chronic phase of the disease, and pentamidin, suramin melarsoprol, and eflornithine against African *trypanosoma* with variable cure rates.
Nose et al. showed that curcumin inhibited African *Trypanosoma in vitro* [38] at around 5 µM for bloodstream forms and around ten times more for procyclic forms of *T. brucei brucei* (the tsetse fly stage). Changtam et al. [34] reported that some curcumin derivatives have potent trypanocidal activity against the *T. brucei brucei* bloodstream form. The most active compound 1,7-bis(4-hydroxy-3-methoxyphenyl)hept-4-en-3-one (**15**) had an EC_{50} value of 0.007–0.053 µM, almost 2-fold more active than the standard veterinary drug diminazene aceturate. The enone structure apparently contributed to the trypanocidal activity [34]. The authors also showed that the curcuminoids had low toxicity to human embryonic kidney cells. As few trypanocidal drugs are currently available, further study is essential to fully exploit the potential role of curcuminoids in the treatment of trypanosomiasis.

Schistosomiasis

Schistosoma spp. are responsible for the most widely distributed flat worm infections known to human kind in developing countries, affecting 200 million people in 74 countries [39]. Their parasitic life cycle starts with the larvae penetrating through the skin of their host. After a larval migration through the lungs, adults parasitize mesenteric blood vessels and liberate embryonated eggs through urine or feces. In water the miracidial stage hatch from the egg, actively looking for intermediate hosts (various genera of snails) within which they transform into sporocysts. There, approximately 1 month later, thousands of cercariae are produced by asexual multiplication, ready to penetrate a new host. The migration of the eggs through the liver, intestine or bladder causes inflammation and scarring. The few drugs available include oxamniquine for the treatment of intestinal schistosomiasis, metrifonate for urinary schistosomiasis, and praziquantel for all forms of schistosomiasis [40,41].
El-Ansary et al. studied the impact of oil extracted from *C. longa* on *Schistosoma mansoni*-infected mice [42]. They showed that although the control drug praziquantel was more effective in lowering worm burden, the *C. longa* extract was more potent in reducing the egg count. The latter was also able to normalize some biochemical parameters (pyruvate kinase, glucose, AMP-deaminase and adenosine deaminase). El-Banhawey et al. reported that an ethanolic extract of *C. longa* administered to *S. mansoni* infected mice, was able to reduce alkaline phosphatase levels and increase the glycogen concentration, when compared to nontreated mice [43]. Interestingly in treated but not infected mice, they also observed higher glycogen reserves. The extract also increased body weight while praziquantel treatment had no effect. Both products were effective in reducing granuloma size in infected mice. Unfortunately in the El-Banhawey study neither the dose nor the route of administration were documented. Shoheib et al. studied the effect of turmeric extracts on freshly shed cercariae from infected *Biomphalaria alexandrina* snails [44]. They observed a decrease in pathogenicity, mean number of deposited eggs, mean diameter of liver granulomas and level of IL-10 gene expression at 10 ppm. In these conditions, they also achieved complete reduction of infectivity of the studied cercariae. Allam [45] infected mice with cercariae of *S. mansoni* and administered curcumin at a dose of 400 mg/kg, intraperitoneally, to circumvent the low rate of absorption via oral administration. At that dose, curcumin reduced worm and egg tissue burden by 31–44%, hepatic granuloma by 79% and liver collagen contents by approximately 40%. Hepatic enzymatic activities, particularly that of catalase, were also restored. Hepatosplenomegaly was improved and eosinophilia decreased. Those improvements were associated with reduced levels of interleukin-12 and tumor necrosis factor alpha. Nevertheless, the IL-10 concentration was not significantly altered. At the immunological level, specific IgG and IgG1 responses against both soluble worm and egg antigens were increased while IgM and IgG2a responses remained unchanged. Magalhaes et al. investigated the activity of curcumin against *S. mansoni* adult worms *in vitro* and showed that their viability and their fecundity decreased at doses ranging from 5–20 µM while doses up to 100 µM were effective at killing worms [46].

Cosmopolitan Parasitosis
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Helminthiasis

Angiostrongylus cantonensis is a nematode (roundworm) commonly found in the pulmonary arteries of rats. Humans are incidental hosts, infected through ingestion of larvae in undercooked snails (the primary intermediate hosts, for developing larvae) or contaminated water and vegetables. Ingested larvae migrate to the central nervous system through the blood stream. They then cause eosinophilic meningoencephalitis, leading to permanent brain and nerve damage or death. This is a serious public health issue in Southeast Asia and the Pacific Basin. In serious cases, treatments are symptomatic and include classic anti-helminthics, such as albendazole and corticoids. Shih et al. with an *A. cantonensis*-induced eosinophilic meningitis model in BALB/c mice, showed that the administration of curcumin moderately reduced the eosinophil count without any larvicidal effect [47]. They argued that the inactivity of curcumin could be due to inefficient passage through the blood-brain barrier.
Toxocara canis is a cosmopolitan helminth parasite found in dogs and cats that can inadvertently infect humans by the ingestion of eggs passed through animal feces. Infected patients present "larva migrans" symptomatology. Albendazole combined with corti-

coids is the first line treatment. Kiuchi et al. isolated cyclocurcumin from the rhizome of *C. longa*. Combined with other curcuminoids it presented some nematocidal activity against the second stage larvae of *T. canis* [48].

It seems then, that against nematodes (at least *Angiostrongylus* and *Toxocara*) there is not enough experimental evidence to support the consideration that curcumin derivatives act as potential nematicides.

Babesiosis

Babesiosis is an infection of red blood cells caused by a parasite of the genus *Babesia (B.)* that is transmitted through the bite of a tick [49]. It is very similar to malaria except that it does not colonize liver cells. Symptoms include fever, fatigue and hemolytic anemia lasting from several days to several months. Treatment commonly combines clindamycin and quinine or atovaquone and azithromycin.

Subeki et al. showed that water extracts of *C. zedoaria* inhibited 50% of parasite growth *in vitro* at approximately 42 µg/mL [50]. Murnigsih et al. also showed that water extracts from the rhizomes of *C. xanthorrhiza* and *C. aeruginosa* Roxb. inhibited more than 60% of the *B. gibsoni* growth at a very high final concentration of 1 mg/mL [10]. *C. xanthorrhiza* was found to be the most active among the extracts. This plant, which is traditionally used in Indonesia in the treatment of malaria, dysentery and cancer, had low toxicity in mice (0.7 g/kg) when administered intraperitoneally. Kasahara et al. isolated zedoalactone derivatives with antibabesial activity against *B. gibsoni* and compared them with the reference drug diminazene aceturate [51] the IC$_{50}$ of which was 0.6 µg/mL, while the zedoalactones were between 3 and almost 30 times less active. Matsuura et al. isolated xanthorrhizol derivatives from *C. xanthorrhiza*, with IC$_{50}$ values ranging from 0.6 µg/mL to 11.6 µg/mL against *Babesia in vitro* [52]. Yamada et al. showed that the 3′-*p*-hydroxybenzaldehyde derivative, the most active compound isolated from the tuber of *C. xanthorriza* had an activity of only one-twelfth of that of the control drug against *B. gibsoni in vitro* (IC$_{50}$ of 50 µM) [53]. Although the *in vitro* activity of some *Curcuma* derivatives seems promising, *in vivo* evidence is lacking and further studies are needed to confirm those results.

Coccidiosis

Cryptosporidium parvum is one of the most common waterborne diseases caused by a coccidian protozoan of the worldwide-distributed genus *Cryptosporidium* [54]. It is localized in the intestines of mammals, via the classical fecal-oral route, through contaminated food or water. In immunocompetent patients, cryptosporidiosis causes an acute self-limiting diarrheal illness during 2 weeks, while in immunocompromised individuals, symptoms are particularly severe and often fatal. As no effective therapy has been developed to date, treatment involves fluid intake for rehydration and pain management.

Shahiduzzaman et al. found that curcumin inhibited more than 95% of *Cryptosporidium parvum* growth at 50 µM in human ileocecal adenocarcinoma cell cultures. Furthermore, doses of 200 µM inhibited the infection of cells by the sporozoite forms [55]. On the contrary, the viability of *C. parvum* oocysts was not impaired after incubation with curcumin.

Toxoplasma gondii is also a cosmopolitan parasite, particularly dangerous to pregnant women and immunocompromised patients, especially those with AIDS. Upon habitation of the *Felidae* species, sexual reproduction takes place, producing oocysts.

These oocysts, when ingested by other mammals, including humans that consume unwashed vegetables or improperly cooked infected meat, transform into tachyzoites which are the motile, asexually reproducing form of the parasite that colonize macrophages. They also transform into cysts, which multiply into bradyzoites. In a letter to the editor of the *Journal of the Egyptian Society of Parasitology,* Abdel-Hady et al. claimed that a methanolic extract of *C. longa* had antitoxoplasma activity (EC$_{50}$ of 0.18 mg/mL) but the authors did not provide any methodological information [56]. In the same journal Al-Zanbagi and Zelai showed that an ethanolic extract of the same plant, previously incubated with tachyzoites of *T. gondii*, and then administered (400 mg/kg) to mice, inhibited parasite growth [57].

Giardiasis

*Giardia lamblia (*also known as *G. duodenalis and G. intestinalis)*, is responsible for the most common cosmopolitan, waterborne intestinal infection [54]. Its life cycle has two stages: flagellated trophozoites attach by their suckers to the surface of the duodenal or jejunal mucosa. Upon passage through the bowel, they transform into ovoid cysts. Those cysts are then excreted with bowel movements and are found in feces. Infection of a new host occurs via contact with cysts in contaminated food or water, or via direct contact with an infected person. Symptoms such as diarrhea, abdominal cramps, flatulence and bloating may lead to malnutrition in chronic disease states. Classic treatments include imidazole derivatives with sufficient water intake for rehydration. Curcumin was tested on the Portland I strain of *G. lamblia* trophozoites [58]. The authors showed that 72 hours post-seeding, 30 µM of curcumin inhibited around 95% of parasite growth. At that dose the adhesion capacity was affected and morphological alterations were similar to those reported for metronidazol. These alterations were characterized by protrusions formed under the cytoplasmic membrane and cellular swelling. The authors concluded that curcumin induced apoptosis-like nuclear staining in a dose- and time-dependent manner. Interestingly the bioavailability of curcumin is advantageous to treat parasites of the digestive tract as most of the ingested curcumin does not diffuse through the digestive barrier [59]. Nevertheless, to the best of our knowledge, no data have been reported on the *in vivo* activity of *Curcuma* derivatives against giardiasis.

Scabies

Scabies is a skin infection, transmitted from one person to another through direct or indirect contact, caused by the arthropod *Sarcoptes (S.) scabiei*, which burrows into skin producing rashes, itching and pain. Classical first line treatment includes permethrine, which may cause allergic reactions. In a clinical trial, neem (*Azadirachta indica*) and turmeric were combined as a paste (4 : 1 neem to turmeric), and applied topically for up to 15 days [60]. This treatment cured around 97% of the people in a cohort of 814 people suffering from scabies. Nevertheless, it remained unclear if turmeric was really active against *S. scabiei* or if its beneficial activity relied on its anti-inflammatory properties.

Conclusion and Perspectives
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Despite international efforts to control parasitic diseases, the reality for numerous patients living in developing countries remains unchanged from decades ago: they still suffer and sometimes die because they cannot afford antiparasitic medicines

with their incomes. Furthermore many drugs are no longer effective due to the emergence of parasite resistance to the treatments. In this context, new, safe, affordable and efficient drugs are needed. An ideal therapeutic candidate must be effective within a short period of time, safe for administration to small children and pregnant women, easy to package, cheap and have a low propensity to generate resistance. *Curcuma* extracts and derivatives could fit these criteria against some parasites, being effective (at least *in vitro*), cheap and well tolerated at very high doses (8 g/day) [61].

Nevertheless, *Curcuma* derivatives are poorly absorbed and are quickly metabolized in rodents and humans [62,63]. This inconvenience could be circumvented by using synthetic related compounds with better absorption, distribution, metabolism, excretion and toxicity properties. Alternatively, the combination of curcumin with a product known to enhance curcuminoid uptake in humans, for example, piperine [63,64], may overcome absorption and metabolism issues, although this concept is controversial [22].

Regarding efficacy, in the case of malaria, we showed that although *Curcuma* derivatives had some antiplasmodial activity *in vitro*, this is not correlated with *in vivo* activity. However, the combination of curcumin with conventional drugs may enhance the effectiveness of curcumin, while simultaneously delaying the emergence of resistance to antimalarial treatments. This strategy could also lower the cost of therapy.

In the case of *Leishmania*, most investigations were conducted on the promastigote forms, and some against amastigotes, but only one study showed some activity *in vivo*. Moreover, sensitivity to curcumin could be demonstrated against the bloodstream stage of *Trypanosoma brucei* only once. This must be confirmed and studies against intracellular life cycle stages must be performed. Against helminths, many studies lack experimental evidence of antiparasitic activity. Nevertheless, it seems that *Curcuma* derivatives are able to reduce symptom severity and egg tissue burden of *Schistosoma*. In the case of *Babesia, in vitro* activity must be supported by *in vivo* studies. This is also the case for *Giardia*. Further studies are required to determine if the use of *Curcuma* derivatives could be of some interest in the anti-coccidial treatment, alone or in association with classical drugs. Finally, in the treatment of scabies in association with neem, *Curcuma* probably acts more as an anti-inflammatory than an anti-*sarcoptes*.

Consequently, taking into account their low bioavailability and the very variable antiparasitic activity of *Curcuma* and derivatives, it is not surprising that this "golden spice" [1] has not been commercialized as an anti-infectious medicine (alone or in combination) at a large scale to date. Generally, pharmaceutical companies are devoted to producing new patentable drugs, rather than unpatentable phytomedicines, although the production of a new formulation could circumvent this problem. Moreover, due to their chemical structures, with a small sized polyphenol and flexible aliphatic chain, curcumin compounds bind, in a non-specific and covalent way to the active sites of many proteins [65], leading to indiscriminate effects. Also as for many natural compounds, *Curcuma* and its derivatives are often claimed to have remarkable properties, while the related experimental procedures often lack methodological accuracy [66,67]. Only meticulous experiments, replicated in different laboratories, and strictly controlled clinical studies will bring definitive evidence of the benefit of *Curcuma* and its derivatives in the therapeutic arsenal against parasites.

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