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Review

Antiparasitic properties of curcumin: A review

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Abstract: Medicinal plants are known as one of the most effective approaches to overcome parasitic infections, which has been used several years ago. *Curcuma longa* (*C. longa)* that is commonly used as a food additive in cooking. Curcumin as the major compound extracted from *C. longa* serves for the various therapeutic and preventive purposes. The present review paper is aimed to investigate the antiparasitic effects of curcumin reported in recent years. The data was collected from several databanks including ISI, Google Scholar, Pubmed, Scopus, and SID (Scientific Information Database, Iran). After a primary study of the retrieved data, the most relevant literature was subjectively classified based on the type of parasite. Then, the effect of curcumin treatment on various parasites was assessed regarding the kind of parasite. According to the results, curcumin manifested a high potential to serve as an effective drug against various parasites. Therefore, further studies in detail on curcumin might offer a new perspective that helps to design efficient formulations for hampering the infections caused by parasites in both human and animals.

Keywords: antiparasitic effects; curcumin; *Curcuma longa*; plant-derived compounds

1. Introduction

To date, numerous studies have been conducting on emerging diseases in developing countries that caused high mortality. Nevertheless, a large number of patients still die due to lack of sufficient medication and also the shortage of health-care service. Besides, emerging types of parasites facilitate recurrence of the parasitic diseases including new drug-resistant variants [1–3].

Turmeric is one of the most consuming medicinal plants belonging to the family Zingiberaceae, *Curcuma* genus, which is commonly known as *Curcuma longa* (*C. longa*). Turmeric extract is thoroughly used in traditional medicine for treating psoriasis, teeth, gum pains, snake bite, and scorpion sting [4]. The therapeutic properties of *C. longa* are attributed to existing the polyphenolic curcuminoid compounds, especially diferuloylmethane or curcumin. This compound commonly presents in the rhizomes of *C. longa* and other *Curcuma* species [5,6]. This compound is a yellow-colored and crystallizable powder with high hydrophobicity that shows poor solubility in aqueous phase [7]. Curcumin possesses the remarkable potential to treat some types of skin inflammations, which in the past was used as an efficient drug for psoriasis therapy [8].

Moreover, curcumin features some biological activity such as anti-inflammation, antioxidant, antiviral, and antimicrobial properties [9]. Due to the low solubility of curcumin in water as well as its instability in some physiological conditions, oral administration results in its poor absorption through the intestinal tract [10]. On the other hand, because of the fast metabolism of curcumin and eliminating its metabolites from the body, its therapeutic effects have significantly declined. As a result, to improve the therapeutic efficiency of the curcumin-containing compound, plenty of attempts has been made aiming to eliminate the biological barriers that might limit its pharmacokinetic properties [11].

As the report of WHO, many of the developing countries are confronting nutritional and health problems as well as especially parasitic infections. Additionally, the prevalence of parasitic diseases is widespread in tropical regions due to the specific climatic conditions facilitating the spread of the parasites [3,12]. In this review, those most common parasites causing the human and animal diseases have been listed in Table 1.

Table 1. Important parasites involved in human and animal diseases.

Parasite type	Disease type	Prevalence rate	Death rate	Reference
leishmania	cutaneous leishmaniasis and visceral leishmaniasis	12 million cases	50,000 cases	[3]
Malaria (*Plasmodium*)	palladium, fever and shivering, periodic fever, and intermittent (recurrent) fever	216 million cases	445,000 cases	[13]
Acanthamoeba castellanii (keratitis)	keratitis and granulomatous amoebic encephalitis (GAE)	Not available	95% of infected patients with GAE	[14,15]
Entamoeba histolytica	bloody diarrhea, amebic dysentery, amebic liver abscesses	40–50 million cases	40,000–100,000 cases	[16]
Trichomonas vaginalis	vaginitis in women, urethritis in man	174 million cases	Not available	[17]
Giardia lamblia	giardiasis: Diarrhea, abdominal pain, and weight loss, vomiting, blood in the stool	280 million individuals annually	Not available	[18,19]
Toxoplasma gondii	Toxoplasmosis is flu-like illness such as muscle aches and tender lymph nodes	200,000 cases of congenital toxoplasmosis occur a year	Not available	[20,21]

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Parasite type	Disease type	Prevalence rate	Death rate	Reference
Neospora caninum	spontaneous abortion in infected livestock similar to *Toxoplasma gondii*	Not available	Not available	[22,23]
Cryptosporidium parvum	acute, watery, and non-bloody diarrhea, respiratory cryptosporidiosis, hepatitis, and cholecystitis	403,000 people in united states in 1993	Not available	[24,25]
Eimeria tenella	Hemorrhagic cecal coccidiosis in young poultry	Not available	Not available	[26,27]
Trypanosoma cruzi	Chagas disease in South America in human, surra, and dourine in horses, and a brucellosis-like disease in cattle	Not available	Not available	[28,29]
Trypanosoma brucei	sleeping sickness in Africa	Not available	Not available	[30,31]
Schistosoma	schistosomiasis is known as a parasitic flatworm with clinical symptoms of diarrhea, bloody stool or blood in the urine	252 million people worldwide in 2015	4400 to 200,000 people	[32,33]
Fasciola hepatica	Gastrointestinal disorders, fever, malaise, urticaria, anemia, jaundice, and respiratory infection	2.5–17 million people and 180 million at risk of infection	Not available	[34]

Various factors, including deforestation, migration as well as promoted tourism industry led to increasing the prevalence of parasitic diseases which reveal the necessity of using effective drugs for treating the patients and carriers [35,36]. *Curcuma* is among the medicinal herbs used with biological properties especially antiparasitic activity [37]. On this basis, the present review is aimed to investigate the antiparasitic properties of the curcumin and its derivatives against some important human and animal parasites.

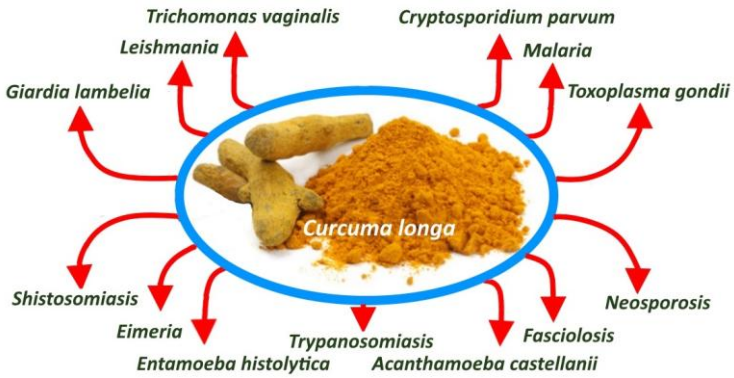

Figure 1. The overview of antiparasitic effects of *C. longa*.

2. Materials and methods

The present review was aimed to scrutiny the use of curcumin and its combination formulations some of its combinations with other drugs for killing or inhibiting the most pathogenic parasites. Some of the related literature published during the 2011–2018 was retrieved from different electronic databases including ISI, Google Scholar, Pubmed, Scopus, and SID. The scientific and general words such as curcumin, *C. longa*, parasite, protozoa, and helminth were searched alone and in combination in these electronic databases. All literature was first analyzed for excluding those original articles that were related to curcumin and parasites. According to the available reports, those parasites, which were treated by various kinds of curcumin formulations were selected to discuss in this review paper.

3. Results

The literature excluded from the crude research was purified regarding relatedness of the experimental and clinical outputs that are focused on the details of the effect of curcumin or extract of *C. longa* (as the crude curcumin) as follows in Table 2.

Table 2. Various formulations of curcumin affecting parasitic pathogens.

Parasite type	Curcumin formulation	Therapeutic effect	Reference
Leishmania major	Combination of Aloe vera extract with animal fat and Turmeric extract	The formulation containing turmeric extract treated cutaneous leishmaniasis in 40% of the patients while those patients who used glucantime were about 32.7%	[38]
Leishmania major	Turmeric extract	Rapid death of promastigotes occurred in the presence of 2 mg/mL of turmeric extract	[39]
Leishmania major and *Leishmania donovani*	Curcumin in Combination with netilmicin, an aminoglycoside antibiotic	Antileishmanial activity of, netilmicin combined with curcumin significantly enhanced compared to when used alone	[40]
Leishmania (L.)amazonensis	The liposomal formulation of turmeric cortex of *Curcuma longa*	The MIC of two formulations (LipoRHIC and LipoRHIWC) of curcumin was obtained 5.5 and 12.5 μg/mL, respectively	[41]
Leishmania major	Curcumin alone and in combination with curcumin + gallium, curcumin + indium, curcumin + Diacethyle	Combination therapy of curcumin with Indium (IC_{50} of 26 μg/mL) and Gallium (IC_{50} of 32 μg/mL) was more potent than curcumin alone and in combination with diacetylcurcum against *Leishmania*	[42]
Leishmania donovani	Nanoformulation of curcumin combined with miltefosine	Combination therapy of curcumin with miltefosine exhibited a synergistic effect on both promastigotes and amastigotes under *in vitro* conditions	[43]
Plasmodium berghei	Curcumin encapsulated to PLGA	Encapsulation of curcumin in PLGA led to increasing parasite suppression bout 56.8% at 5 mg/kg of nanoformulation which was higher than in free curcumin (40.5%) at 10 mg/kg	[44]

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Parasite type	Curcumin formulation	Therapeutic effect	Reference
Plasmodium vivax	Ethanol extracts of *Curcuma caesia* and *Curcuma longa*	These extracts showed significant parasitemia inhibitions against Chloroquine-resistant *P. vivax*	[45]
Plasmodium berghei	Curcumin-arteether combination	Prevents recrudescence through immunomodulation in *Plasmodium berghei* in mice	[46]
Plasmodium falciparum	Curcumin (In silico simulation study)	The high affinity of curcumin obtained for binding with HGPRT of PfHGPRT as two virulence factors in malaria progression	[47]
Plasmodium berghei	Curcumin alone	CD8 + T cell and pRBC sequestration into the brain and blood-brain barrier (BBB) breakdown	[48]
Plasmodium falciparum	Curcumin-loaded in FΔF nanotubes	Showed of *Plasmodium falciparum* inhibition (IC_{50}, 3.0 μM) as compared to free curcumin (IC_{50}, 13 μM)	[49]
Plasmodium yoelii	Curcumin bound chitosan nanoparticles	Can cross the mucosal barrier intact, inhibited parasite lysate in a dose-dependent manner in a lower IC_{50} value than chloroquine	[50]
Plasmodium berghei	Nanoformulation of curcumin	inhibit *P. falciparum* ten-fold more than its native counterpart in vitro	[51]
Plasmodium falciparum	Curcumin alone	Exhibited high antimalarial activity (IC_{50} ~10 μM) and lowered apoptosis in bEnd.3, a endothelialpolyoma cell line	[52]
Plasmodium falciparum	Curcumin analogs	In silico and in vitro study showed various functional groups of curcumin and its analogs against the PfATP6 protein	[53]
Acanthamoeba castellanii	Ethanol extract of *Curcuma longa*	Found to be more effective than chlorhexidine as a common antiseptic agent	[54]
Entamoeba histolytica	Curcumin- metronidazole combination	65.5% of parasite trophozoites died in the presence of curcumin- metronidazole combination	[55]
Trichomonas vaginalis	Curcumin alone	100% eradication of all trichomonal cells within 24 h was reached at a concentration of 400 μg/mL curcumin	[56]
Giardia lamblia	Curcumin alone	Curcumin inhibited *Giardia* proliferation, disrupted the cytoskeletal structures of trophozoites in the dose-dependent mode	[57]
Giardia	Curcumin-loaded chitosan nanoparticles	The parasite was successfully eradicated from stool and intestine by curcumin-Cs nanoparticles treatment	[58]
Toxoplasma gondii	Curcumin alone	Curcumin inhibited the enzymatic activity of recombinant TgGlo1 and the parasitic propagation in vitro	[59]
Neospora caninum	Curcumin alone	Curcumin exhibited inhibitory activity with 50% growth inhibitory concentration (IC50) of 1.1 ±0.4	[22]

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Parasite type	Curcumin formulation	Therapeutic effect	Reference
Cryptosporidium parvum	Curcumin alone	The anti-cryptosporidial and antioxidant activity of curcumin against *C. parvum* were confirmed	[12]
Eimeria tenella	Dietary Curcuma longa	*C. longa*-induced intestinal transcriptome was mostly associated with genes mediating anti-inflammatory effects	[60]
Eimeria tenella	Curcumin alone	At high concentrations had considerable effects on sporozoite viability and morphology	[61]
Elmira tenella	Curcumin alone	Curcumin showed a significantly lower percentage of sporozoite invasion than the untreated control	[62]
Trypanosoma cruzi	Curcumin combined with benznidazole	Combination therapy with curcumin-benznidazole showed a drastic reduction in parasitemia, mortality, cytokines (IFNγ, IL-4, and MIP-1) and myocardial inflammation	[28]
Trypanosoma cruzi	Curcumin alone	Curcumin inhibited parasite invasion in fibroblasts. Besides, curcumin modulated signaling pathways involved associated with inflammation, oxidative stress, and apoptosis	[63]
Trypanosoma cruzi	Curcumin analogs formulations	Curcuminoid as a curcumin analog showed a potent trypanocidal activity	[29]
Trypanosoma cruzi	Curcumin alone	Curcumin blocked calcium-dependent NFATc1 transcription, reduced COX-2, and mPGES-1 expression, and suppressed PGE2 production in ET-1 in the parasite-infected cardiomyocytes	[64]
Schistosoma mansoni	Turmeric diet	Turmeric reduced *Schistosoma* burden, granuloma size and ameliorated the pathology effects of liver infected by the parasite.	[32]
Schistosoma mansoni	Curcumin alone	Curcumin-induced DNA fragmentation and increased the expression of *SmCASP3/7* transcripts that involved in apoptosis in *Schistosoma* parasitic cells	[65]
Schistosoma mansoni	Curcumin alone	Curcumin increased several genes involved in embryogenesis and oogenesis such as Notch and TGF-β	[66]
Fasciola gigantica	Curcumin alone	A significant decrease was observed in the expression of glutathione-S-transferase, and superoxide dismutase	[67]
Fasciola species	Curcumin-nisin nanoparticulate	Ovicidal activity of the curcumin-nisin nanoparticles was confirmed against the *Fasciola* species	[68]

4. Discussion

4.1. Leishmania

Leishmaniasis refers to parasitic diseases caused by *Leishmania* species that transmitted by the certain types of sandflies bite. Based on the pathological features, this disease is classified into three types, cutaneous, mucocutaneous and visceral leishmaniasis. Cutaneous type is identified with lesions on the skin, the mucocutaneous type is differentiated with lesions on the skin, mouth, and nose, while the visceral type in addition to skin lesions, is diagnosed by high fever, low red blood cells, spleen swelling and liver enlargement causing immune deficiency in some cases and it may lead to death [69]. In the last decades, Sodium stibogluconate and pentamidine are the first-generation medication used for treating leishmaniasis [70].

However, miltefosine, paromomycin, and liposomal amphotericin B, either individually or in combined form, are the selected medication used for emergency cases as well as prevention of emersion of resistance in new *Leishmania* strains [1]. In this regard, several formulations of curcumin were examined to treat the leishmaniasis.

Bahrami et al. (2011) showed that among the patients treated by a herbal compound known as plant juice combination, an ingredient of which is *C. longa*, the healing period for the ulcers caused by cutaneous leishmaniasis (major leishmaniasis) in a 63 to 76-day interval was about 40%; while, among those patients receiving only glucantime (*Meglumine antimonate*), the ulcer healing period was 32.7% [38]. Hosseini et al. (2012) reported that curcumin at concentration of 2 mg/L of total turmeric extract, compared to the concentration of 0.2 mg/L, would quickly kill the promastigotes of major leishmaniasis in 88 hours, indicating the higher quantitative effect of turmeric extract in comparison to liquorice (*Glycyrrhiza glabra*) as well as its parasiticidal potential at lower dosages [39]. In another study by Tiwari et al. (2017), it was shown that the combination of nanocurcumin and miltefosine could be considered as a new strategy for treatment of the *Leishmania*-induced diseases. The compound treatment (miltefosine and nanocurcumin) in vitro, in addition to its synergistic effects on promastigotes and amastigotes, leads to the increased phagocytic activity as well as increased reactive metabolites of oxygen and nitrogen. Furthermore, it was shown that administration of the miltefosine-curcumin nanoformulation yielded a parasitic inhibition of 85% ± 1%; thus, this treatment approach, regarding its *p*-value of $p < 0.001$, was proved to have considerably higher effectiveness compared to the administration of miltefosine alone against *Leishmania donovani* [43]. Amaral et al. (2014) studied anti-*leishmania* activity of two nonpolar fractions obtained from the turmeric cortex (TC) and turmeric without cortex (TWC). The fractions were exposed to *Leishmania amazonensis* for determining the inhibition potency against this parasite. For this purpose, the TC and TWC extracts were dissolved in hexane, and then the resulting solution was incorporated in a liposome, the products of which were named *LipoRHIC* and *LipoRHIWC*. The best minimum inhibitory concentration (MIC) for LipoRHIC at sub-inhibitory concentration of 2.75 μg/mL was obtained equal to IC_{50} value of 0.4 μg/mL for 48 h treatment, indicating the treatment's effect on emersion of membrane blebs, cell shrinkage, and surface deformation, which were accompanied by mitochondrial inflammation as well as vacuolization and complete intracellular disorganization [41]. Another study conducted by Fooladvand et al. (2013) reported that indium curcumin with IC_{50} value of 26 μg/mL for 24 h treatment was shown to be more effective than curcumin, gallium curcumin, and indium curcumin against leishmaniasis [42].

4.2. Malaria

Malaria is among the most important parasitic diseases, which commonly appears as an acute, in some cases malignant, and sometimes long-lasting infection associated with intermittent fever and shivering, anemia, and enlarged spleen [13]. Currently, chloroquine, sulfadoxine/pyrimethamine (SP), as well as artemisinin and its derivatives are considered as the appropriate treatments for malaria; nonetheless, drug resistance and toxicity, for most of the available drugs such as chloroquine and SP have presented serious challenges to the treatment of malaria [71].

In this regard, the researchers are increasingly attempting to find an antimalarial drug and reduce drug resistance using *Curcuma* extract as well as curcumin and its derivatives. Busari et al. (2017) showed that the use of curcumin-PLGA would yield higher parasiticidal property (56.8%) against *P. berghei* compared to pure curcumin (40.5%); also, curcumin-PLGA at lower concentrations was shown to be better than pure curcumin regarding health and anti-plasmodium activities [44]. The ethanolic extracts *C. cassia* and *C. longa* resulted in a significantly reduced parasitemia within the ranges of 5.8–75.6% and 2–29.8%, respectively, against the blood stage of *P. vivax*. According to the obtained results, fractions of this plant featured antimalarial potential, and the *C. caesia* had the lowest parasitemia (24.4%) in addition to the inhibition of invasion of malaria parasite *P. vivax* to the cells [45]. Studies have shown that the simultaneous use of curcumin and artemisinin has been considered as a new synergistic compound for the treatment of *P. berghei*, and has also exhibited its potential for improving the immune system against recurrence of *P. berghei* in BALB/c mice [72]. Cui et al. (2007) showed that edible administration of curcumin (100 mg/kg) during a 5-day regime reduced 80–90% of the blood parasitemia in the mice infected by *P. berghei* [73]. The compound treatment with AC (arteether-curcumin) applied on the ECM (experimental cerebral malaria) mice proved to be a promising approach, such that the AC was capable of reversing all of the understudy parameters including inflammatory responses, TCD8+, and obstructive red blood cells that move toward the brain vessels and break the brain-blood obstacle. In addition to postponing the mice's death for 15–20 days, curcumin resulted in the reduced parasitemia and reduced secretion of the cytokines IFN-γ and TNF-α as well as suppression of the TCD8+ in brain and spleen [48]. Among the peptide groups responsible for drug delivery, including dehydrophenylalanine (ΔPhe), phenylalanine-α,β-dehydrophenylalanine (FΔF), arginine-α,β-dehydrophenylalanine (RΔF), valine-α,β-dehydrophenylalanine (VΔF), and *methionine-α,β*-dehydrophenylalanine (MΔF), which were combined with various nanoparticles and nanotubes under the same conditions, the FΔF exhibited higher loading capacity (almost 68% W/W) than curcumin compared to other peptides.

Furthermore, in the case of (IC_{50}, 13 μM), this peptide group showed a higher parasite reproduction inhibition potential than pure curcumin in the *P. falciparum*-infected mice. The curcumin-containing dipeptide nanoparticles demonstrated a good system for drug delivery to the cells and inhibition of malaria parasite reproduction [49]. The study conducted by Kunwittaya et al. (2014) addressed the potential role of curcumin in parasite elimination and endothelial protection in case of cerebral malaria. According to the results, curcumin exhibited a high malaria growth inhibition level (IC_{50} ~10 μM) and reduced the endothelial apoptosis of brain vessels by 60%, while the pretreatment endothelial apoptosis was 79.6% [52]. In another study, edible curcumin nanoparticles were administrated to mice that infected by *P. berghei.* This treatment resulted in complete elimination of parasites from the patient's bodies and subsequently increased survival time of the infected mice from eight days to two months [51]. Furthermore, curcumin-chitosan

nanoparticles (CCsNPs) enhanced the lifetime of mice which infected by *P. yoelii*. An *in vitro* experiment showed that CCsNPs could inhibit the growth of parasite through inducing the synthesis of hemozoin [50].

4.3. Acanthamoeba castellanii

A. castellanii is one of eight major protozoa causing severe keratitis in contact lens users. It can also cause skin lesions in patients with compromised immune systems [14]. Although medications against *Acanthamoeba* are commonly exploited, the complete eradication of infection seems to be a serious challenge when the parasite forms of the drug-resistant cysts. Therefore, pharmacotherapy of the *Acanthamoeba* or its cysts could emerge the new drug-resistant parasites [74].

The study of El-Sayed et al. (2012) on the antiparasitic effect of ethanolic extract of *C. longa* against *A. castellanii*, two inhibition doses was determined in 48 h and 72 h with MIC of 1 g/mL and 100 mg/mL, respectively. This study showed that the ethanolic extract of *C. longa* had an inhibitory effect on the growth of the *A. castellanii* cysts with a MIC of 1 g and 100 mg/mL. The cysticidal effect of *C. longa* might be due to the curcumin, which is one of the major elements responsible for biological actions [54].

4.4. Entamoeba histolytica

Intestinal protozoa known as *Entamoeba histolytica* causes amoebiasis. As one of the main parasitic pathogens, this protozoan is estimated to infect 40–50 million individuals, among whom only 10% manifest the acute form of the disease leading to an annual mortality rate of 40000–100000 cases [16]. Metronidazole is an appropriate anti protozoan medication against the amoebic colitis; nevertheless, due to its fast absorption in case of oral infusion, it cannot be effective against the luminal trophozoites. Additionally, nearly 40–60% of the treatment is associated with drug-resistance of the parasite, so that elimination of the luminal parasites necessitates administration of paromomycin or diloxanide furoate for the patient [75]. Moreover, all of the drugs of this type are associated with some side effects such as nausea, headache, loss of appetite (anorexia), and metallic taste [2]. Therefore, researchers are still attempting to find new drugs with high therapeutic potential as well as low side effects.

In a study in this regard, the researchers compared the amoebicidal capability of curcumin on *E. hisolytica* and its synergic effects with those of metronidazole. The best inhibitory effect of curcumin was achieved at concentration of 300 μM in 24 hours so that the parasite growth inhibition power was 65.5% and only 28.8% of the trophozoites could survive. Curcumin caused some morphological alterations in trophozoites, reduced parasite size, as well as reduced parasite uniformity. Such changes were examined using SEM microscope leading to the conclusion that the synergistic effect of curcumin and metronidazole would enhance the antiparasitic effects of these two medications together [55].

4.5. Trichomonas vaginalis

Trichomoniasis is a sexually transmitted protozoan disease in human reproductive system which is caused by *T. vaginalis*. This disease is estimated to have an annual morbidity rate of 174 million

cases worldwide. The drug-resistance engendered by metronidazole, which is the medication for *T. vaginlis*, necessitates the use of alternative drugs against this type of parasite [17].

In another study, Watcher et al. (2014) addressed the role of curcumin derived from *C. longa* in the treatment of *T. vaginalis*. For this purpose, the strains with different sensitivities to metronidazole were exposed to curcumin treatment at concentrations of 400, 200, and 800 μg/mL to compare with metronidazole. As a result, the best concentrations of curcumin with EC50 (73.0–105.8 μg/mL) and EC90 (64.9–216.3 μg/mL) at 3, 6, and 24 h showed that the concentration of 400 μg/mL could accomplish complete (100%) elimination of the parasites in 24 h [56]. Regarding the lower toxicity of curcumin at higher concentrations compared to metronidazole that is associated with systemic side effects in case of oral intake, and since the curcumin-containing drug (*CurcumallR*) is used topically for trichomoniasis treatment, it has been used with no toxic effect on the treatment of oral lesions [76].

4.6. Giardia lambelia

G. lambelia is a parasite with global distribution that infects nearly 280 million individuals annually. It is the most prevalent parasite in developed countries. In Africa, Asia, and Latin America, there are 200 million individuals with giardia infection, 500000 cases of which have clinical symptoms [19]. Metronidazole is one of the best medications for *Giardia* infection, yet it is associated with some side effects, such as nausea and metallic taste in mouth, and should not be taken with alcohol. Nitazoxanide (Alinia) is the liquid form of a drug prescribed for children, but it is also associated with side effects such as nausea, tympanites (meteorism), and yellow eyes [77]. Regarding the side effects of these drugs as well as their complications for pregnant women, specifically in the first trimester of pregnancy, it seems necessary to find and use some new medications for treating the *Giardia* infections.

Gutierrez et al. (2017) showed the role of curcumin in the inhibition of *Giardia*. At 3 and 15 μM of curcumin, the cellular structure of *Giardia* was destroyed and then caused deformation of the parasite membrane, flagella, and abdominal wall. Based on the results of this study, tubulin is the main target of curcumin in destroying the *Giardia* lamblia trophozoite [57]. Additionally, the nanoparticles of silver, chitosan, and curcumin were also used for the treatment of giardiasis. As indicated by findings of this study, the use of these three types of nanoparticles combined together (nAg + Ncs + nCur) was effectively efficient compared to the separate use of them against *Giardia*, since the intestines and stool could be successfully cleaned and disposed of parasites while application of nAg + nCur for treatment of *Giardia* yielded a reduction of 91% in the parasites [58].

4.7. Toxoplasma gondii

T. gondii can afflict a wide range of warm-blooded animals including humans, livestock, and domestic animals. Clinically, this parasite causes some deficiencies in a growing embryo, which may lead to abortion in some cases, as well as opportunistic infections in immune-deficient patients and transplantation patients [20]. In acute forms of toxoplasmosis, two drugs known as pyrimethamine (Daraprim) and sulfadiazine are commonly used for medication. However, the pyrimethamine-induced side effects, such as bone marrow suppression and hepatotoxicity (liver

toxicity), reveal the necessity of seeking to find new treatment alternatives for toxoplasmosis treatment purposes [78].

Goo et al. (2015) reported that curcumin could inhibit the glyoxalase-1, thus plays an effective role in the anti-toxoplasmosis activity. By preventing the enzymatic activity of the recombinant TgGlo1, the inhibitory effect of curcumin resulted in the parasite proliferation in the *T. gondii* culture medium at IC_{50} 38.3 ± 0.9 μM, leading to inhibition of the glyoxalase system metabolic pathway, which is necessary for the parasite to survive and live. These findings exhibited the role of curcumin against toxoplasmosis metabolic pathways [59].

4.8. Neosporosis

Neosporosis is caused by *N. caninum* and is a serious disease among cattle and dogs. This protozoon can cause abortion and stillbirth among cows [23]. As Qian W et al. (2015) showed in their study, curcumin was capable of preventing proliferation and growth of the parasites in human foreskin fibroblast cells infected by *Neospora* parasite at IC_{50} value of 1.1 ± 0.4 μM [22].

4.9. Cryptosporidium parvum

C. parvum is one of the most important water-transmitted protozoans causing parasitic diseases, which is scattered throughout the world. It is transmitted through the oral-fecal route as well as contaminated water and foods. In patients with immune-deficiency, *cryptosporidiosis* can cause severe self-limiting diarrhea for two weeks, the treatment of which includes fluid consumption (for rehydration) and pain control [24]. *Nitazoxanide* is the drug recommended by FDA as the medication for treating diarrhea in immunocompetent patients, but its effectiveness among immunocompromised patients is still unknown [79]. The lack of an established treatment method for patients with immune deficiency, it seems necessary to seek new treatments.

In *Cryptosporidium*-infected mice, in addition to the reduction in tissue lesions as well as some oocytes on the villi in both ileum and jejunum regions, curcumin could yield the increased TAC (total antioxidant capacity) and decreased MDA (malondialdehyde) in the infected mice [12].

4.10. Eimeria

Parasites of this genus are capable of producing spores and releasing immature oocytes from the intestine's walls. In the poultry industry, *E. tenella* has caused health problems, decreased production efficiency, and increasingly elevated drug-resistance against antibiotics [27]. In one of the studies in this regard, different concentrations of curcumin were used to investigate the life cycle and morphology of the sporozoites. In this work, the curcumin concentrations of 100 and 200 μM reduced the sporozoite infection by 41.6% and 72.8%, respectively [61]. Additionally, daily *C. longa*-supplemented feeding of the broilers in a poultry farming led to reduction in the Eimeria-induced inflammatory reactions and intestinal damages [60]. In another study, the use of VAC (carvacrol, cinnamaldehyde, and capsicum oleoresin) edible compound yielded the improved immunity in the experimentally *E. tenella*-infected chickens [26].

4.11. Trypanosomiasis

Trypanosoma is a flagellated protozoan member of the genus *kinetoplastids*. It is transmitted through biting or blood-feeding invertebrates and can cause some human diseases such as *Chagas* (caused by *T. cruzi*), which is mainly in Central and South America, and *sleeping sickness* (caused by *T. brucei*) mainly in Africa [80]. Pentamidine is a medication used in the primary stage of treatment for the sleeping sickness caused by *T.b.gambiense* infection, while other drugs (such as eflornithine, melarsoprol, suramin, and nifurtimox) are used for treating the African trypanosomiasis [81]. Also, benznidazole is the drug used for the treatment of *Chagas* disease, yet in case of acute form of the disease, nifurtimox is used as medication for treatment purposes [82]. Nevertheless, since the drugs used for treatment, including *nifurtimox*, has not been approved by FDA, it seems necessary to seek for new herbal medicines for treatment.

Curcumin has the potential for obstruction, Ca^{2+}-dependent NFATc1 duplication activities, induction of COX-2 and mPGES-1, production of PGE2 in excited ET-1 and parasite-infected myocytes, reduction of the level of prostaglandins of cardiomyocytes, as well as incurrence of disorders in PGE2/EP4 receptors [64]. In another study, examination of the morphological structure of the parasite using an electron microscope showed that the use of curcumin with IC50 value of 10.13 μM and dimetoxycurcumin (DMC) with IC50 value of 11.07 μM could result in cytoskeletal alterations in the parasite's epimastigote [29].

4.12. Schistosomiasis

Shistosomiasis is one of the most common parasitic diseases throughout the world, which is caused by a parasite called *Schistosoma*. There are about 207 million cases of this disease in 76 countries from around the world, mainly in developing countries, and meanwhile, 800 million individuals are exposed to the risk of infection [33].

There are only a few drugs for the treatment of schistosomiasis, among which metrifonate is used for the urinary schistosomiasis and *praziquantel* is prescribed for all forms of schistosomiasis [83]. The emergence of drug resistance in this disease reveals the necessity of further studies aiming to find new medications.

Hussein et al. (2017) conducted a study focusing on the potential role of *C. longa*, either dissolved lonely in olive oil or in combination with praziquantel, in treating the *schistosomiasis mansoni* (*S. mansoni*). According to the results, the use of *C. longa* combined with praziquantel led to the reduced worm burden and complete elimination of adult worms of *S. mansoni* in the studied mice, significantly reduced size of granuloma, a considerable improvement in worm-induced pathological damages in general, and a mild reduction in the inflammation among the mice [32]. Additionally, another study was conducted on the effect of curcumin on induction of apoptosis in the *S. mansoni* worms, the results of which indicated that curcumin caused DNA damages and fragmentation, increased expression of the *SmCASP3/7* transcripts, and activation of Caspase 3 in male-female worm couples. Moreover, curcumin could increase the superoxide anion and activate the superoxide dismutase (SOD), which led to the oxidation of proteins in *S. mansoni* worms, indicating that induction of apoptotic-like events would increase the oxidative stress among the worms followed by their death [65]. Morias et al. (2013) showed that curcumin resulted in the separation of male and female *S. mansoni* worms, infertility of eggs, reduced oviposition, reduced

lifetime of worms, and finally their death. Besides, it affected the expression of those genes that are involved in embryogenesis and oogenesis such as Notch and TGF-β. Curcumin affects the oviposition and growth of the parasite eggs by repressing the transcripts of these genes [66].

4.13. Fasciolosis

The species of liver trematodes, such as *F. hepatica* and *gigantica*, can cause fasciolosis and are widely scattered throughout the world, mainly among the ruminants and among the sheep in particular. *F. parasites* infect the humans less than livestock. Both young and adult forms of these parasites can be treated by triclabendazole [34]. Ullah et al. (2017) showed that the use of curcumin at concentration of 60 μM resulted in a significantly reduced motility of the *F. Gigantica* worms ($p < 0.05$), disordered egg shedding, disrupted tegument, severely eroded spines in posterior region revealing the syncytium, as well as the significantly reduced activity of the GST enzyme at concentration of 60 μM ($p < 0.01$) [67].

Moreover, the ovicidal properties of the curcumin-nisin nanoparticles against the *Fasciola* species were assessed. Accordingly, at the highest concentration of the curcumin-nisin nanoparticles, i.e., 5 mg/mL, the fasciola eggs had the lowest hatching rate (41.7%) compared to other groups and the control group, as well as the albendazole positive control group with hatching rate of 45.1%. Besides, the curcumin-nisin medication had no toxic effect on the mice's sperms and only killed the fasciola parasite eggs [68].

5. Conclusion

The present review manifested the potential of curcumin as a common food seasoning with the hopes of increasing the knowledge of society about the various advantages of consumption of *C. longa*. Thus, further studies in formulations of curcumin and its derivatives could help to control, prevent, and treat the parasitic diseases.

Conflict of interest

All authors declare no conflicts of interest in this review paper.

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