Antiparasitic properties of curcumin: A review

Kourosh Cheraghipour¹, Abdolrazag Marzban¹, Behrouz Ezatpour¹*, Sayyad Khanizadeh² and Javad Koshki³

¹ Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran
² Hepatitis Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran
³ Lorestan Provincial Veterinary Service, Khorramabad, Iran

* Correspondence: Email: bezatpour@gmail.com.

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.**

<table>
<thead>
<tr>
<th>Parasite type</th>
<th>Disease type</th>
<th>Prevalence rate</th>
<th>Death rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>leishmania</em></td>
<td>cutaneous leishmaniasis and visceral leishmaniasis</td>
<td>12 million cases</td>
<td>50,000 cases</td>
<td>[3]</td>
</tr>
<tr>
<td><em>Malaria</em> (Plasmodium)</td>
<td>palladium, fever and shivering, periodic fever, and intermittent (recurring) fever</td>
<td>216 million cases</td>
<td>445,000 cases</td>
<td>[13]</td>
</tr>
<tr>
<td><em>Acanthamoeba castellanii</em> (keratitis)</td>
<td>keratitis and granulomatous amoebic encephalitis (GAE)</td>
<td>Not available</td>
<td>95% of infected patients with GAE</td>
<td>[14,15]</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td>bloody diarrhea, amebic dysentery, amebic liver abscesses</td>
<td>40–50 million cases</td>
<td>40,000–100,000 cases</td>
<td>[16]</td>
</tr>
<tr>
<td><em>Trichomonas vaginalis</em></td>
<td>vaginitis in women, urethritis in man</td>
<td>174 million cases</td>
<td>Not available</td>
<td>[17]</td>
</tr>
<tr>
<td><em>Giardia lamblia</em></td>
<td>giardiasis; Diarrhea, abdominal pain, and weight loss, vomiting, blood in the stool</td>
<td>280 million individuals annually</td>
<td>Not available</td>
<td>[18,19]</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Toxoplasmosis is flu-like illness such as muscle aches and tender lymph nodes</td>
<td>200,000 cases of congenital toxoplasmosis occur a year</td>
<td>Not available</td>
<td>[20,21]</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Parasite type</th>
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</tr>
</thead>
<tbody>
<tr>
<td><em>Neospora caninum</em></td>
<td>spontaneous abortion in infected livestock similar to <em>Toxoplasma gondii</em></td>
<td>Not available</td>
<td>Not available</td>
<td>[22,23]</td>
</tr>
<tr>
<td><em>Cryptosporidium parvum</em></td>
<td>acute, watery, and non-bloody diarrhea, respiratory cryptosporidiosis, hepatitis, and cholecystitis</td>
<td>403,000 people in united states in 1993</td>
<td>Not available</td>
<td>[24,25]</td>
</tr>
<tr>
<td><em>Eimeria tenella</em></td>
<td>Hemorrhagic cecal coccidiosis in young poultry</td>
<td>Not available</td>
<td>Not available</td>
<td>[26,27]</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>Chagas disease in South America in human, surra, and dourine in horses, and a brucellosis-like disease in cattle</td>
<td>Not available</td>
<td>Not available</td>
<td>[28,29]</td>
</tr>
<tr>
<td><em>Trypanosoma brucei</em></td>
<td>sleeping sickness in Africa schistosomiasis is known as a parasitic flatworm with clinical symptoms of diarrhea, bloody stool or blood in the urine</td>
<td>Not available</td>
<td>Not available</td>
<td>[30,31]</td>
</tr>
<tr>
<td><em>Schistosoma</em></td>
<td>schistosomiasis is known as a parasitic flatworm with clinical symptoms of diarrhea, bloody stool or blood in the urine</td>
<td>252 million people worldwide in 2015</td>
<td>4400 to 200,000 people</td>
<td>[32,33]</td>
</tr>
<tr>
<td><em>Fasciola hepatica</em></td>
<td>Gastrointestinal disorders, fever, malaise, urticaria, anemia, jaundice, and respiratory infection</td>
<td>2.5–17 million people and 180 million at risk of infection</td>
<td>Not available</td>
<td>[34]</td>
</tr>
</tbody>
</table>

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*.](image)
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>
<thead>
<tr>
<th>Parasite type</th>
<th>Curcumin formulation</th>
<th>Therapeutic effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Leishmania major</em></td>
<td>Combination of Aloe vera extract with animal fat and Turmeric extract</td>
<td>The formulation containing turmeric extract treated cutaneous leishmaniasis in 40% of the patients while those patients who used glucantime were about 32.7%</td>
<td>[38]</td>
</tr>
<tr>
<td><em>Leishmania major</em></td>
<td>Turmeric extract</td>
<td>Rapid death of promastigotest occurred in the presence of 2 mg/mL of turmeric extract</td>
<td>[39]</td>
</tr>
<tr>
<td><em>Leishmania major</em> and <em>Leishmania donovani</em></td>
<td>Curcumin in Combination with netilmicin, an aminoglycoside antibiotic</td>
<td>Antileishmanial activity of, netilmicin combined with curcumin significantly enhanced compared to when used alone</td>
<td>[40]</td>
</tr>
<tr>
<td><em>Leishmania (L.)amazonensis</em></td>
<td>The liposomal formulation of turmeric cortex of <em>Curcuma longa</em></td>
<td>The MIC of two formulations (LipoRHIC and LipoRHIWC) of curcumin was obtained 5.5 and 12.5 µg/mL, respectively</td>
<td>[41]</td>
</tr>
<tr>
<td><em>Leishmania major</em></td>
<td>Curcumin alone and in combination with curcumin + gallium, curcumin + indium, curcumin + Diacethyl</td>
<td>Combination therapy of curcumin with Indium (IC₅₀ of 26 µg/mL) and Gallium (IC₅₀ of 32 µg/mL) was more potent than curcumin alone and in combination with diacetylcurcum against <em>Leishmania</em></td>
<td>[42]</td>
</tr>
<tr>
<td><em>Leishmania donovani</em></td>
<td>Nanoformulation of curcumin combined with miltefosine</td>
<td>Combination therapy of curcumin with miltefosine exhibited a synergistic effect on both promastigotes and amastigotes under <em>in vitro</em> conditions</td>
<td>[43]</td>
</tr>
<tr>
<td><em>Plasmodium berghei</em></td>
<td>Curcumin encapsulated to PLGA</td>
<td>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</td>
<td>[44]</td>
</tr>
</tbody>
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<th>Therapeutic effect</th>
<th>Reference</th>
</tr>
</thead>
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<tr>
<td><em>Plasmodium vivax</em></td>
<td>Ethanol extracts of <em>Curcuma caesia</em> and <em>Curcuma longa</em></td>
<td>These extracts showed significant parasitemia inhibitions against Chloroquine-resistant <em>P. vivax</em></td>
<td>[45]</td>
</tr>
<tr>
<td><em>Plasmodium berghei</em></td>
<td>Curcumin-arteether combination</td>
<td>Prevents recrudescence through immunomodulation in <em>Plasmodium berghei</em> in mice</td>
<td>[46]</td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em></td>
<td>Curcumin (In silico simulation study)</td>
<td>The high affinity of curcumin obtained for binding with HGPRT of PfHGPRT as two virulence factors in malaria progression</td>
<td>[47]</td>
</tr>
<tr>
<td><em>Plasmodium berghei</em></td>
<td>Curcumin alone</td>
<td>CD8 + T cell and pRBC sequestration into the brain and blood-brain barrier (BBB) breakdown</td>
<td>[48]</td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em></td>
<td>Curcumin-loaded in FΔF nanotubes</td>
<td>Showed of <em>Plasmodium falciparum</em> inhibition (IC\textsubscript{50}, 3.0 μM) as compared to free curcumin (IC\textsubscript{50}, 13 μM)</td>
<td>[49]</td>
</tr>
<tr>
<td><em>Plasmodium yoelii</em></td>
<td>Curcumin bound chitosan nanoparticles</td>
<td>Can cross the mucosal barrier intact, inhibited parasite lysate in a dose-dependent manner in a lower IC\textsubscript{50} value than chloroquine</td>
<td>[50]</td>
</tr>
<tr>
<td><em>Plasmodium berghei</em></td>
<td>Nanoformulation of curcumin</td>
<td>Inhibit <em>P. falciparum</em> ten-fold more than its native counterpart in vitro</td>
<td>[51]</td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em></td>
<td>Curcumin alone</td>
<td>Exhibited high antimalarial activity (IC\textsubscript{50}~10 μM) and lowered apoptosis in bEnd.3, a endothelialpolyoma cell line</td>
<td>[52]</td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em></td>
<td>Curcumin analogs</td>
<td>In silico and in vitro study showed various functional groups of curcumin and its analogs against the PfATP6 protein</td>
<td>[53]</td>
</tr>
<tr>
<td><em>Acanthamoeba castellanii</em></td>
<td>Ethanol extract of <em>Curcuma longa</em></td>
<td>Found to be more effective than chlorhexidine as a common antiseptic agent</td>
<td>[54]</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td>Curcumin- metronidazole combination</td>
<td>65.5% of parasite trophozoites died in the presence of curcumin- metronidazole combination</td>
<td>[55]</td>
</tr>
<tr>
<td><em>Trichomonas vaginalis</em></td>
<td>Curcumin alone</td>
<td>100% eradication of all trichomonial cells within 24 h was reached at a concentration of 400 μg/mL curcumin</td>
<td>[56]</td>
</tr>
<tr>
<td><em>Giardia lamblia</em></td>
<td>Curcumin alone</td>
<td>Curcumin inhibited <em>Giardia</em> proliferation, disrupted the cytoskeletal structures of trophozoites in the dose-dependent mode</td>
<td>[57]</td>
</tr>
<tr>
<td><em>Giardia</em></td>
<td>Curcumin-loaded chitosan nanoparticles</td>
<td>The parasite was successfully eradicated from stool and intestine by curcumin-Cs nanoparticles treatment</td>
<td>[58]</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Curcumin alone</td>
<td>Curcumin inhibited the enzymatic activity of recombinant TgGlo1 and the parasitic propagation in vitro</td>
<td>[59]</td>
</tr>
<tr>
<td><em>Neospora caninum</em></td>
<td>Curcumin alone</td>
<td>Curcumin exhibited inhibitory activity with 50% growth inhibitory concentration (IC\textsubscript{50}) of 1.1 ± 0.4</td>
<td>[22]</td>
</tr>
</tbody>
</table>

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<thead>
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<th>Curcumin formulation</th>
<th>Therapeutic effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cryptosporidium parvum</em></td>
<td>Curcumin alone</td>
<td>The anti-cryptosporidial and antioxidant activity of curcumin against <em>C. parvum</em> were confirmed</td>
<td>[12]</td>
</tr>
<tr>
<td><em>Eimeria tenella</em></td>
<td>Dietary <em>Curcuma longa</em></td>
<td><em>C. longa</em>-induced intestinal transcriptome was mostly associated with genes mediating anti-inflammatory effects</td>
<td>[60]</td>
</tr>
<tr>
<td><em>Eimeria tenella</em></td>
<td>Curcumin alone</td>
<td>At high concentrations had considerable effects on sporozoite viability and morphology</td>
<td>[61]</td>
</tr>
<tr>
<td><em>Elmira tenella</em></td>
<td>Curcumin alone</td>
<td>Curcumin showed a significantly lower percentage of sporozoite invasion than the untreated control</td>
<td>[62]</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>Curcumin combined with benznidazole</td>
<td>Combination therapy with curcumin-benznidazole showed a drastic reduction in parasitemia, mortality, cytokines (IFNγ, IL-4, and MIP-1) and myocardial inflammation</td>
<td>[28]</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>Curcumin alone</td>
<td>Curcumin inhibited parasite invasion in fibroblasts. Besides, curcumin modulated signaling pathways involved associated with inflammation, oxidative stress, and apoptosis</td>
<td>[63]</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>Curcumin analogs formulations</td>
<td>Curcuminoid as a curcumin analog showed a potent trypansomidal activity</td>
<td>[29]</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>Curcumin alone</td>
<td>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</td>
<td>[64]</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>Turmeric diet</td>
<td>Turmeric reduced <em>Schistosoma</em> burden, granuloma size and ameliorated the pathology effects of liver infected by the parasite.</td>
<td>[32]</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>Curcumin alone</td>
<td>Curcumin-induced DNA fragmentation and increased the expression of <em>SmCASP3/7</em> transcripts that involved in apoptosis in <em>Schistosoma</em> parasitic cells</td>
<td>[65]</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>Curcumin alone</td>
<td>Curcumin increased several genes involved in embryogenesis and oogenesis such as Notch and TGF-β</td>
<td>[66]</td>
</tr>
<tr>
<td><em>Fasciola gigantica</em></td>
<td>Curcumin alone</td>
<td>A significant decrease was observed in the expression of glutathione-S-transferase, and superoxide dismutase</td>
<td>[67]</td>
</tr>
<tr>
<td><em>Fasciola species</em></td>
<td>Curcumin-nisin nanoparticulate</td>
<td>Ovicidal activity of the curcumin-nisin nanoparticles was confirmed against the <em>Fasciola</em> species</td>
<td>[68]</td>
</tr>
</tbody>
</table>
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 (IC50, 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 (IC50 ~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 protozoan 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. histolytica* 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. vaginalis*, 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 lamblia*

*G. lamblia* 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 eflorentiflume, 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 dimethoxycurcumin (DMC) with IC50 value of 11.07 µM could result in cytoskeletal alterations in the parasite’s epimastigote [29].

4.12. **Schistosomiasis**

Schistosomiasis 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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