

Anti-Parasitic Activity of Zingiber officinale (Ginger): A Brief Review

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Abstract

Zingiber officinale (*Z. officinale*) is a perennial herb with several medicinal properties. Development of modern drugs from *Z. officinale* can be emphasized for the control of various diseases. The feasibility of using *Z. officinale* to treat parasite infections has received considerable interest nowadays. Therefore, this review focused on the anti-parasitic activity of *Z. officinale*. Method of this literature search was conducted on PubMed, Elsevier Scopus database and Google Scholar with no limitation on language or year of publication databases. *Z. officinale* was found to have a significant antihelmintic activity against *Schistosoma mansoni*, *Toxocara canis*, *Dirofilaria immitis*, *Angiostrongylus cantonensis*, *Anisakis simplex*, *Hymenolepis nana* and hydatid cysts either *in vitro* or *in vivo*. Also, it has an anti-protozoal effect against *Toxoplasma gondii*, *Giardia lamblia*, *Trypanosoma brucei brucei* and *Blastocystis* species. Additionally, it was found to have insecticidal, molluscicidal and anti-leech effects.

Keywords: *Zingiber officinale*; Active constituents; Anti-parasites

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Introduction

Human infections that caused by endoparasites, including protozoa, nematodes, trematodes, and cestodes, affect more than 1–2 billion of people, particularly in tropical developing countries and lead to several million deaths every year [1]. Due to the lack of a licensed vaccine for any human parasitic disease together with a lack of affordable, safe and effective drugs for some diseases or the parasites resistant to the available synthetic

therapeutics, it is important to search for alternative sources of anti-parasitic drugs [2]. Despite recent advances that are helping to fuel drug discovery efforts, such as the sequencing of several parasites genomes and the establishment of public–private partnerships to specifically focus on tropical disease drug discovery and development, there are numerous challenges facing research in this area particularly, the large cost associated with progressing compounds, together with the poor financial incentives to big pharma [3, 4].

The search for bioactive plants which can be used as unconventional anti-parasitic drugs has received considerable attention in recent times and it is estimated that 20,000 species of higher plants are used medicinally throughout the world. Natural product screening provides the chance to discover new molecules of unique structure with high activity and selectivity which can be further optimized by semi- or fully synthetic procedures [5]. Success in natural products research is conditioned by careful plant selection, based on various criteria such as chemotaxonomic data, information from traditional medicine, field observation, or even random collection [6].

A number of medicinal plant extracts have been screened for their anti-parasitic activities and have proven to be more effective than the currently used therapies [7-11]. These extracts often interfere with central targets in parasites, such as DNA (intercalation, alkylation), membrane integrity, microtubules and neuronal signal transduction [2, 8, 9].

Zingiber officinale as natural herbal medication

Z. officinale (ginger) (Figure 1) is a perennial herb belonging to the family *Zingiberaceae*. It is a pungent, aromatic spice which adds a special flavor and zest to the food. *Z. officinale* is widely distributed in tropical Asia and it is the most common spice, used all over the world. More than 60 active constituents are known to be present in ginger, which have been broadly

divided into volatile and nonvolatile compounds. Volatile components include hydrocarbons mostly monoterpenoid hydrocarbons and sesquiterpene that impart distinct aroma and taste to ginger. While, nonvolatile compounds include gingerols, shogaols, paradols, and zingerone [12].

Figure 1: *Zingiber officinale* A) Plant, B) rhizome [10]



Numerous experimental and clinical trials have proven ginger for its range of therapeutic activities such as antiemetic, stomachic, expectorant, antibacterial, antifungal, antidiabetic, hypolipidaemic nephroprotective, hepatoprotective, cytotoxic, antioxidant, immunostimulant, anticarcinogenic and anti-inflammatory activities. Besides, it possesses biological actions like increasing respiratory burst, phagocytic activity, and disease resistance against pathogens [13]. Moreover, it behaves as an appetite stimulant, anxiolytic, antithrombotic, radiation protection, and inhibits the reactive nitrogen species which are important in causing Alzheimer's disease and many other disorders. All these biological activities are attributed to phytochemical constituents of this medicinal plant [12].

Anti-parasitic activity of *Zingiber officinale*

Several *in vitro* and *in vivo* studies have proven that *Z. officinale* and its constituents exert significant nematocidal, cestocidal, trematocidal, anti-protozoal, insecticidal, molluscicidal and anti-leech effects (Figure 2). There is speculation that the mechanism of action of ginger may be both central and peripheral, i.e., anticholinergic and antihistaminic [14]. Neal [15] suggested that nematode muscles contain excitatory neuromuscular junctions with acetylcholine as the neurotransmitter. Gilani and Ghayur [16] reported that ginger exhibits gastrointestinal pro-kinetic activity via activation of cholinergic receptors. Iqbal et al. [17] suggested

that the cholinergic component of ginger is responsible for its anthelmintic activity.

Figure 2: Anti-parasitic activity of *Zingiber officinale*



1- Nematocidal effect of *Zingiber officinale*

Nematocidal activity of *Z. officinale* was reported against *Angiostrongylus cantonensis* and *Anisakis simplex* larvae. *Angiostrongylus cantonensis* is a parasitic nematode which causes angiostrongyliasis, the most common cause of eosinophilic meningitis in Southeast Asia and the Pacific Basin. *Anisakis simplex* is a parasitic nematode, which present in fish and other marine mammals. Human get infected by consuming infected raw seafood and diseases is called anisakiasis. From the roots of *Z. officinale*, [6]-gingerol, [10]-gingerol, [10]- shogaol, [6]-shogaol and hexahydrocurcumin were isolated. These compounds exhibited larvicidal activity against the larvae of the above mentioned nematodes by direct killing or reducing spontaneous movement. It was revealed that [10]-gingerol showed higher larvicidal than mebendazole and albendazole and resulted in to100% lethality against the larvae of *Anisakis simplex* [18, 19].

Human toxocariasis is an accidental parasitic disease due to infection by larval stages of *Toxocara canis* and *Toxocara cati*, the common roundworms of dogs and cats, respectively. Two well-defined clinical syndromes are classically recognized: visceral larva migrans (a systemic disease caused by larval migration through major organs) and ocular larva migrans (a disease limited to the eyes and optic nerves) [20]. *Z. officinale* seemed to be effective as albendazole against *T. canis* infection. It had a significant inhibitory effect on the larval recovery rates in the liver, lungs, and brains after 28th days post-infection compared to the infected controls. *Z. officinale* improved the induced pathological changes by *Toxocara* in the studied organs that regressed to near normal picture after its combination with albendazole. In addition, treatment with *Z. officinale* separately or in combination with albendazole revealed a significant improvement in the levels of Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline Phosphatase (ALP) as an indication of its hepatoprotective effect [11].

Dirofilaria immitis is a parasitic nematode that is common in domestic and wild animals. Human dirofilariasis is transmitted by the bite of an infected mosquito and represents as pulmonary and subcutaneous nodules [21]. Isolated extracts from the rhizome of ginger have anthelmintic activity against *Dirofilaria immitis* *in vivo* and *in vitro* [22, 23].

Additionally, crude powder and aqueous extract of dried ginger were used in sheep naturally infected with mixed species of gastrointestinal nematodes, including *Trichostrongylus colubriformis*, *Haemonchus contortus*, *Oesophagostomum columbianum*, *Trichostrongylus axei*, *Trichuris ovis* and *Strongyloides papillosus* to investigate its anthelmintic activity [17]. Also, the nematocidal activity of ginger was studied on the poultry nematode, *Ascaridia galli*. It was concluded that ginger in all used concentrations exhibited a higher wormicidal effect [24].

2- Trematocidal effect of *Zingiber officinale*

Schistosomiasis *mansoni* is a tropical helminthic disease characterized by parasite egg-induced granulomatous inflammation. Liver and intestinal fibrosis is a major sequel to granulomatous schistosomiasis *mansoni* mostly responsible for portal hypertension, formation of esophageal varices, and intestinal bleeding of infected humans. Several investigations

have been undertaken regarding the trematocidal activity of *Z. officinale* against *Schistosoma mansoni* (*S. mansoni*).

It was found that *Z. officinale* displayed some degree of anti-schistosomal activity by reducing of *S. mansoni* eggs output (53.8 %), worm burden (16.5 %) and the size of liver granuloma (66.35%) in the infected animals [25]. Also, Mostafa et al. [26] assessed the effect of *Z. officinale* aqueous extract, on the oxidative status, antioxidant defense system and liver pathology of *S. mansoni* infected mice. Infection by *S. mansoni* exhibited a suppression of liver antioxidant capacity, and depleted reduced glutathione content, superoxide dismutase, and catalase activities. Also, the hepatic lipid peroxidation was elevated in *S. mansoni* infected mice. *Z. officinale* treatment at a dose of 500 mg/kg, orally administered daily for five weeks from the 5th week post-infection showed improvement in the liver functions; the hepatic total protein, ALT and AST.

3- Cestocidal effect of *Zingiber officinale*

Hymenolepis nana is the most common tapeworm in humans. It is also known as the dwarf tapeworm. The infection is transmitted by fecal-oral rout resulting in non-specific symptoms such as abdominal pain, loss of appetite, diarrhea, flatulence, weight loss, irritable behavior, anal pruritus and delayed growth. Some constituents from the roots of ginger were found to exert a cestocidal effect against *Hymenolepis nana* *in vitro* and *in vivo*. It was demonstrated that [10]-shogaol and [10]-gingerol exhibited dose- and time-dependent cestocidal effect with respect to spontaneous parasite oscillation and peristalsis movement. Additionally, in morphological examination, *Hymenolepis nana* adult worms destroyed by these constituents, especially in scolox or arc or triangle proglottid segment [27].

Moazeni and Nazer [28] investigated the effectiveness of methanolic extract of *Z. officinale* on the protoscolices of hydatid cyst, a larval stage of *Echinococcus granulosus*. *Echinococcosis* (hydatid disease), a zoonosis, is characterized by frequent hepatic involvement. Scolicidal activity of *Z. officinale* extract at a concentration of 25, 50 and 100 mg/mL was after 60, 40 and 30 min of its application respectively. Also, Baqer et al. [29] determined *in vivo* efficacy of ethanolic extract of *Z. officinale* as antiprotoscolices.

4- Anti-protozoal effect of *Zingiber officinale*

Protozoal infections are of great importance in public health because of their high prevalences, distribution and their effects on the population. The drugs currently used to treat these diseases have serious side effects, so it is relevant to look for new pharmacological alternatives. From this point of view, anti-protozoal activity of *Z. officinale* was evaluated by several investigators.

Toxoplasma gondii, an obligate intracellular protozoan, is the most frequent protozoan causing opportunistic infections in immunocompromised individuals resulting in the infection dissemination that causing serious complications in the form of encephalitis, myocarditis and pneumonitis with higher mortality rates. Choi et al. [30] evaluated the anti-protozoal effect of Ginger root Extract (GE) and GE/F1 (fraction 1 obtained from GE) against *Toxoplasma gondii* both *in vitro* and *in vivo*. They demonstrated that GE/F1 not only induces anti-*Toxoplasma gondii* effects causing the inactivation of apoptotic proteins in infected host cells through the direct inhibition of *Toxoplasma gondii* but also has anti-parasitic properties which inhibit inflammatory cytokine secretion *in vivo*.

The potential therapeutic effect of dichloromethane ginger extract on *Giardia lamblia* infection in albino rats was studied. This protozoon is responsible for intestinal infection and diarrhea that may lead to nutritional deficiencies, especially in children. Ginger treatment caused reduction of *Giardia lamblia* fecal cyst and trophozoites counts. Also, exposure to this extract revealed evident improvement of intestinal mucosal damage produced by *Giardia lamblia* infection and direct structural injury to the trophozoites [31].

In addition, *in vivo* anti-protozoan effect of *Z. officinale* extract on experimentally infected mice with *Blastocystis spp.* was evaluated by Abdel-Hafeez et al. [32]. Anti-protozoal activity of this herb was determined by monitoring *Blastocystis* shedding in stools and histopathological changes of the intestine of infected mice. Additionally, its antioxidant effect (via measuring the level of malondialdehyde (MDA) production) and Nitric Oxide (NO) production were assessed. Treatment of infected mice with ginger reduced the shedding of cysts significantly compared to the infected untreated group. As well, histopathological examination revealed that *Blastocystis* was frequently observed within the lumen, at the tip of the epithelium, and/ or infiltrated in an

enterocyte in the infected group without treatment compared to that of the infected treated ones. Furthermore, treatment of infected mice with ginger reduced the elevated levels of NO and MDA

Human African trypanosomiasis, also known as sleeping sickness, is a vector-borne parasitic disease. It is caused by infection with protozoan parasites belonging to the genus *Trypanosoma*. Antitrypanosomal effect of methanolic extract of *Z. officinale* on *Trypanosoma brucei brucei*-infected Wistar mice was investigated by Kobo et al. [33]. Administration of methanolic extract of *Z. officinale* increased body weight and survival time of mice infected with *Trypanosoma brucei brucei*. It also reduced the level of parasitemia in infected mice.

5- Insecticidal effect of *Zingiber officinale*

Various species of mosquitoes are important insect vectors of human diseases including *Anopheles* (a vector of malaria), *Culex* (a vector of lymphatic filariasis) and *Aedes aegypti* (a vector of dengue) [34]. Vector borne diseases not only cause high levels of morbidity and mortality but also inflict great economic loss and social disruption on developing countries. *Z. officinale* showed insecticidal, ovicidal and repellent activities against *Anopheles stephensi*, *Aedes aegypti*, and *Culex quinquefasciatus* [35]. This mosquito larvicidal activity was attributed to *Z. officinale* compounds; (4)-gingerol, (6)-dehydro -gingerdione and (6)-dihydrogingerdione that were isolated from its rhizome [36].

6- Molluscicidal effect of *Zingiber officinale*

Many aquatic snails act as intermediate hosts for the trematodes. *Biomphalaria alexandrina* is the snail vector of *S. mansoni*. Control of this intermediate host disrupts the life cycle of the parasite, stopping the transmission of infection. However, the high costs and toxicity of synthetic molluscicides have stimulated renewal interest in plant molluscicides [37]. *Z. officinale* was reported to have molluscicidal and antischistosomal effect against *S. mansoni* miracidia and cercariae [38]. Bakry et al. [39] studied the effect of *Z. officinale* on the survival rate, egg production, electrophoresis analysis, biochemical aspects of *Biomphalaria alexandrina* snails infected with *S. mansoni*. Their results showed that a rapid decline in survival rate and egg production of infected snails with *S. mansoni* exposed to ginger and also, showed that the glucose concentrations in infected snails exposed to ginger were increased in the hemolymph, while soft tissue glycogen decreased. In addition, the activities of glycogen

phosphorylase, succinate dehydrogenase and glucose-6-phosphatase in homogenate tissues of infected snails were reduced in response to exposure to ginger.

7- Anti-leech effect of *Zingiber officinale*

Limnatis nilotica (*L. nilotica*), an internal leech is commonly found in Southern Europe, North Africa, and the Middle East. It attaches itself to the mucous membranes of the pharynx, nasal cavity, nasopharynx, and oesophagus. Patients infested with *L. nilotica* often present with epistaxis, hemoptysis, or hematemesis [40]. The anti-leech effects of the methanolic extract of *Z. officinale* with levamisole were evaluated. It was found that methanolic extract of *Z. officinale* (600 mg/ml) killed leeches at an average time of 33.3 ± 11.4 min while, the average time for death with levamisole (100 mg/ml) was 10.7 ± 1.9 min [41].

In another experimental study, anti-parasitic effect of *Z. officinale* on *L. nilotica* leech was evaluated. After treating the leeches with *Zingiber officinale* (32×10^4 ppm) and the positive controls with chlorine (4×10^6 ppm), formalin 37% (4×10^3 ppm) and savlon (4×10^3 ppm) for 30 min, the mean death time of *L. nilotica* was measured. The mean death time for *Z. officinale* was 24 ± 4.07 min and for chlorine, savlon and formalin were 1.62 ± 0.51 , 3.37 ± 1.9 , 5.12 ± 1.9 min, respectively. These results offer an opportunity for using ginger medicinal plant as anti-parasitic and disinfectant [42].

Conclusion

Z. officinale has an effective anti-parasitic activity against several parasites and can be used for prevention of drug resistant parasitic diseases. However, further evaluation is necessary to isolate the active constituents, and determines their toxicity, side effects and pharmaco-kinetic properties.

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