Herbal Medicines Journal **Winter 2017; Vol. 2, No. 1:43-9**
DOI: 10.22087/HMJ.V1I2.594

Review Article

Anti-toxoplasmosis activity of herbal medicines: Narrative review

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Received: 18.10.2016; Accepted: 02.01.2017

Abstract

Toxoplasmosis is known as a parasitic protozoan disease which is globally distributed. It is caused by *Toxoplasma gondii*. Sulfadiazine and pyrimethamine are two medicines utilized as parts of a standard therapy for toxoplasmosis. Since the curative medicines currently used in the treatment of toxoplasmosis bring about serious host toxicity, conducting a research on an effective and new substance characterized by relatively low toxicity is required urgently. The naturally derived herbs and plants' extracts as alternative medicines are getting increasing interest in the world. Various studies have been conducted so far concerning the application of herbal medicines for the treatment of toxoplasmosis, but a research on relatively effective and low toxic substances is still needed. Due to increasing interest in the use of natural products to treat of infectious diseases, we conducted this study. In this review, we have summarized the information of those herbal medicines which are reported to have anti-*Toxoplasma gondii* activity. We referred to the information databases of Medline, PubMed, Scopus and Google Scholar. The keywords include a combination of *T.gondii* and some words associated with herbal medicines and natural products.

Keywords: Anti-*Toxoplasma gondii* effect, Natural products, Plant extracts, Toxoplasmosis

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Please cite this article as: Arab-Mazar Z, Kheirandish F, Rajaeian S. Anti-toxoplasmosis activity of herbal medicines: Narrative review. Herb Med J. 2017;2(1):43-9.

Introduction

Toxoplasma gondii (*T.gondii*) is an obligate intra cellular protozoan parasite which can infect a wide range of hosts. It is reported that approximately one-third of the world's population are infected to this parasite (1). Toxoplasmosis causes chronic infection with parasite cyst formation in tissues among immune-competent individuals, but when the immune system of individual wanes, e.g., in cases of AIDS or chemotherapy patients, T.gondii reacts and causes acute infection and toxoplasmosis clinical manifestation (2, 3).

Sulfonamide and pyrimethamine are the effective drugs used nowadays for the treatment of toxoplasmosis (4). These drugs work primarily by blocking or destroying thetoxoplasma folic acid metabolic pathways (5). Moreover, toxoplasmosis in pregnant women in the current treatment guideline is the administration of spiramycin which has high concentration in placental tissue, hence decreases the risk of fetaltransmission (6). According to previous

studies, these treatments may have adverse reactions, such as the suppuration of bone marrow, teratogenic effects in the first trimester of pregnancy, hematological reaction, embryopathesis and gastrointestinal disorders (4, 7, 8). Therefore, studding and developing a novel and safe efficient drug with low toxicities seems urgent and vital.

Cultural knowledge about herbal medicines has a key role in discovering the novel and new natural products with chemotherapeutic properties (9-11). The use of herbal medicines in developed countries is still popular among most people due to historical and cultural reasons despite the fact that they have access to modern medicines (12, 13). Historically, natural products and their compounds have been the most productive sources for the treatment of a wide range of diseases especially infectious diseases (14-16).

Recently, new studies have emphasized on complementary and alternative medicines against parasitic disease management (17, 18) such as *T.gondii*. Therefore, this study is going to review and summarize the efficacy of medicinal plants which are used and reported to have anti-*T. gondii*a ctivity throughout the world. This research can contribute to future therapeutic choices and studies.

***Eurycoma longifolia* Jack**

E. longifolia Jack, from the Simaroubaceae family and locally known as " Tongkat Ali" or " Pasakbumi" which is kind of traditional medicine and commonly prescribed as a febrifuge and a remedy for dysentery, glandular swelling and fever (19, 20). *E. longifolia* is found in both primary and secondary forests associated with both evergreen jungles and those in which trees shed their leaves annually in east and southeast of Asia including Burma, Indochina, Thailand, Malaysia and Philippines.

NowrojiKavith et al., have found in a study on the roots of *E. longifolia* Jack that extraction of this plant has a significantly anti-*T. gondii* activity. They have observed that *E. longifolia* fractions significantly inhibited *T. gondii* growth even at low concentration.They also suggested the *E. longifolia* might be a potential candidate as an alternative to Clindomycin for the treatment of toxoplasmosis (21).

***Balsamocitrus camerunensis* L (Rutaceae)**

The family of Rutaceae consist of about 1500 species which are principally found in temperate and tropical regions (22).Rutaceae species are used as traditional medicines for the treatment of elephantiasis, gonorrhoea, malaria and abdominal pain (23-25).

Emmanuel Ngeufa Happi et al., have reported in a study the isolation and characterization of five known compounds isolated from the CH2Cl2/MeOH extracts of the roots of the plant *B.camerunensis*, namely marmin1, imperatorin2, xanthoxyletin3, 6, 7-Dimethoxycoumarin 4 and1-hydroxy-3-methoxy-acridone 5, as well as their intracellular anti-*toxoplasma* activity growth and proliferation. They have reported that some of the isolated compounds have significant anati-*T.gondii* activity with approximately 46.44% inhibition of parasite growth for compound 4 and 82.12 % for compound 3 (26).

Thai Piperaceae plants

Thai Piperacea plants include approximately 1000 species of herbs which are found in tropical areas such as India and Thailand (27, 28). These plants are used as a traditional Thai medicines for treating different diseases such as ameliorating stress andcancer,as well as inthe improvement of digestion.They also have anti-malarial effect (29-31).The pharmacological properties of piperaceae plants enable them to have antimicrobial, antioxidant, gastroprotective, anticancer and also in some cases anti-leishmanial, and anti-malarial activities (32-34).

ArpronLeesombunet al., have done a study to evaluate the anti-toxoplasmosis effect of ethanol extracts from Thai piperaceae plants (*P. betle*, *P. nigrum* and *P. sarmentosum*) in vitro and in vivo. Their data and analysis indicated thatcompared to other extracts,*P. betle* extract has greater potential to be used as a medicine for the treatment of toxoplasmosis (35).

***Bunium persicum* (Bioss)**

Bunium persicum (Bioss) belongs to Apiaceae family which is known as a " ZireKohi" in Persian (36). The plant, especially its seed,was used in traditional medicinein the form of carminative as an anti-spasmodic and antiepileptic medicine (37). Other studies have also indicated the anti-inflammatory and antimicrobial activity of *B. persicum* essential oil (38-40).

Tavkkoli Kareshk et al., are the only researchers in whose study the anti-*toxoplasma* effects of this plants has been evaluated. They assessed the prophylactic

and therapeutic efficacy of this plant's essential oil on infected mice. Their analysis showed that *Buniumpersicum* in the concentration of 0.1 ml/kg reduced significantly mean number of parasite compared to control one (41).

Vanilin

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is a compound which is isolated from the bean and pod of tropical vanilla orchid. In addition, vanilla is used in food and relevant industries for the synthesis of different agrochemicals, antifoaming agents and pharmaceutical products (42). This substance has also been the subject of several scientific investigations during recent years, like identification of antioxidant properties (43), antimicrobial activity (44-46), and antimutagenic (47, 48) as well as anticarcenogenic actions (49).

It is known from the work of Oliveira et al., (50) that vanillin compound has antiprotozoal activity. They examined antioxidant and the anti-*toxoplasma* activity of vanillin and compared it with resorcinarence compounds. They have found that unlike resvan, vanillin is capable of having anti-toxoplasma activity.They stressed the importance of vanillin acting to combat parasite infection specially toxoplasmosis.

***Ginkgo biloba* (Ginkgaceae)**

Ginkgo biloba (Ginkgaceae) is kind of Chinese traditional herbal medicine derived from the gingko tree. This medicine has been used over a thousand years. In a study carried out by Chen et al., the anti-*T.gondii* activity of the Ginkgolic (GAS) acids (51) was evaluated. The toxicity of GAS and azithromycin was compared in this study. They have determined that GAS inhibited the growth of *T. gondii*at concentrations lower than 12.5 µ g/ml. While azithromycin inhibited at concentration as low as 3.13 µ g/ml. The researchers recommended more studies, especially in vivo research, to be done concerning the impact or effectiveness of GAS in the treatment of toxoplasmosis.

Olive (*Olea europaea*)

Maslinic acid (2R,3-dihydroxyolean-12-en-28-oic acid) is a triterpenoid compound related to oleanolic acid which is found in numerous plants (52-55) especially in considerable amount in fruit and leaves of *Oleaeuropaea* (56, 57).

Luis M et al.,evaluated in their study the action of maslinic acid (2R,3-dihydroxyolean-12-en-28-oic acid), a pentacyclic derivative present in the pressed fruits of the olive (*Oleaeuropaea*), against the tachyzoites of *T.gondii* (58). They found the parasites which were treated with maslinic acid gliding motility and ultra-structural alterations. Maslinic acid workedthe same as other protease inhibitors which are described in the articles as inhibitors of growth and intracellular replications of *T.gondii* (59, 60). It blocks the entry of parasite into the cell.

***Sephora flavescens* Aiton**

Sephora flavescenc Aiton is another Chinese traditional medicine capable of antimicrobial, antiviral, antitumor, anti-inflammatory and anti-parasitic activity (61-65). It has been observed that the methanolic extract of *Sephora flavescens* has high anti-*T.gondii* activity (66). Also other studies demonstrated that ethanol extract of *Sephora flavescens* had high efficacy in reducing the replication of *Toxoplasma*, but unfortunately the chemical composition and mechanism of this herbal medicine is not clear yet (67). Recently, pharmacological studies on this substance have found clinical application. Oxymatrine (OM) and matrine (ME) which are present in *Sephora flavescens* have major functions (68).

Currently a few studies analyzed the anti-*toxoplasma* effect of *Sephora* alkaloid. Zhang et al., have evaluated therapeutic efficacy of these two *Sephora* alkaloid, oxymatrine (OM) and matrine (ME), for their role in controlling toxoplasmosis infection (69). They analyzed the effect of both OM and ME *in vivo* in acutely *T.gondii* infected mice and observed that both substances could significantly decrease the number of tachyzoites in the peritoneal cavity of infected mice. Azadirachtaindica, Cinnamonnumcamphora, Lippiamultiflora, Vernoniacolorata, Guierasenegalensis, Combretummicranthum, Ximeniaamericana, Cochlospermumplanchonii and Sidaacuta.

These are West African Traditional Medicines which are collected in Ivory Coast. Their extractions were prepared from different parts of the plants (Table 1) (70). Benoit-Vical et al., (71) evaluated all these herbal anti- *toxoplasma* activities. The in vitro activity of plant extracts against *T. gondii* was assessed on

Table 1: The in vitro activity of plant extracts on *T. gondii* was assessed on MRC5 tissue cultures and was quantified by enzyme-linked immunoassay.

Plant	Family	Part Used	Inhibition of T. gondii growth IC 50 (mg/L)
Azadirachta indica	Meliaceae	Stem, leaf	> 1,000
Cinnamonnum camphora	Lauraceae	Cortex	789
Lippia multiflora	Verbenaceae	Leaf	201
Vernonia colorata	Composeae	Stem, leaf	17
Guiera senegalensis	Combretaceae	Stem, leaf	351
Combretum micranthum	Combretaceae	Stem, leaf	217
Ximenia americana	Oleaceae	Stem, leaf	> 1,000
Cochlospermum planchonii	Bixaceae (Cochlospermaceae)	Tubercle	> 1,000
Sida acuta	Malvaceae	Flower, leaf	> 1,000

MRC5 tissue cultures and was quantified by enzyme-linked immunoassay (Table 1).

They have observed that *Azadirachtaindica, Cinnamonmumcamphora, Cochlospermumplanchoni, Sidaacuta andXimeniaamericana*, had almost no inhibitory effect against Toxoplasma. A marked inhibition of Toxoplasma growth among above extracts was observed in Vemoniacolorata. Herein, we showed that *V. colorata*may had potential therapeutic interest for toxoplasmosis as it strongly inhibited Toxoplasma growth at concentrations that were nontoxic for cell cultures. *L. multiflora* and *C. micranthum* aqueous extracts were found to have moderate but significant inhibitory effects on Toxoplasma growth. Despite these antimicrobial activities, the use of aqueous extracts of C. *micranthum* or *L. multiflora* to cure toxoplasmosis may be limited because the IC, values against T. gondiiwere high (> 100 mg/L) and probably not achievable in vivo (71).

***Zingiber offcinale* (Ginger)**

Zongiber officinale Roscoe, commonly known as ginger, has been widely used both in herbal and folk medicine. It is also used as spice in food in many countries (72). In addition, these natural products have been used in Asia for the treatment of human diseases like infectious diseases such as common cold, cough, dyspepsia, diarrhea, and headache (73). Moreover, it has been reported that Ginger is capable of having antimicrobial, anticancer and anti-inflammatory activities (74-77).

WonHyung Choi et al., evaluated the antiphrastic effect of ginger root extract against *T.gondii*in vitro and in vivo (78). Ginger root extract strongly inhibited the proliferation of C6 cells (Rat C6 glioma cells) which were infected by *T. gondii* and compared with sulfadiazine. Moreover, vivo tests have been done on Balb/c to determine the extract effect on mice survival and the production of cytokine such as interferon gamma INF-γ and interleukin 8 (IL-8). The results show that extract courses improved the survival of infected mice and also inhibited the inflammatory response.

***Artemisia annua L* (Asteraceae)**

Artemisia annua L. is an annual herb belonging to the family of Asteraceae that is endemic to the northern parts of China (79). Its active compound, artemisinin, is generally present in the leaves and flowers.

Taísa Carrijo de Oliveira et al.,evaluated the effect of *Artemisia annua* on in vitro and in vivo *T.gondii* infection (80).Dried herb of *A. annua* infusion was prepared and tested in human foreskin fibroblasts (HFF) or mice that were infected with the parasite and then it was compared with sulfadiazine treatment.*In vivo* experiments show that A. annua effectively controls infection by *T. gondii* since its extraction of low toxicity and its inhibitory action is used directly against the parasite which can be used as a tolerated therapeutic tool.

***Myristica fragrans* Houtt (Nutmeg)**

Nutmeg (*Myristica fragrans* Houttuyn) is the seed kernel inside the fruit and mace is the lacy covering

(aril) on the kernel (81). Some studies have been done to evaluate anthelmintic, hepatoprotective and anti-inflammatory, as well as aphrodisiac properties of nutmeg. Its capability of being used as insecticide and the possibility of utilizing it in the treatment of rheumatism, diarrhea, asthma, atherosclerosis and flatulence has been evaluated too (82-84).

In a study conducted by Suthagar Pillai et al., the anti-parasitic activity of *Myristica fragrans* Houttuyn's essential oil against *T.gondii* parasite was evaluated (85). They extracted oil from nutmeg and investigated its *in vitro* cytotoxicity on Vero cell line and its anti-parasitic activity against *T. gondii*. They concluded that nutmeg's essential oil showed strong anti-*T.gondii* activity beside low toxicity against normal cell line.

Conclusion

Although tropical parasites such *as T.gondii* affect hundreds of millions of people worldwide, they have been largely neglected for drug development, because people in these area are poor (86). Therefore, developingcheap, reliable and affordable drugs for the treatment of these infections is vital and important. The limited efficacy of drugs against this infection, their side effects and the potential appearance of resistance strains implies that it is essential to carry out research on novel drugs.

Acknowledgment

The authors appreciate all people who helped in this research.

Conflict of Interest

The authors declare that they have no conflict of interest.

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