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Toxoplasmosis and anti-*Toxoplasma* effects of medicinal plant extracts-A mini-review

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ABSTRACT

Toxoplasmosis is a globally distributed parasitic protozoan disease, caused by *Toxoplasma gondii*. The infection can result in more severe symptoms with potentially life-threatening in case of immunocompromised individuals. Sulfadiazine and pyrimethamine are the two drugs used as a part of standard therapy for toxoplasmosis. Researchers have demonstrated the therapeutic effects of medicinal plants for toxoplasmosis, which can be used as an alternative to standard drug therapy with reduced side effects. Traditional herbal plants are used by people to cure a large number of parasitic disorders. This review provides new insights into various medicinal plants that are used traditionally for the treatment of toxoplasmosis and other parasitic infections, which can be useful as an alternative treatment option for *Toxoplasma gondii* infections.

1. Introduction

Toxoplasma gondii (*T. gondii*) is one of the most successful parasitic protozoa that cause an important zoonosis worldwide. Although, all warm-blooded animals are vulnerable to the infection, the final hosts of this pathogen are felids. The environmentally resistant oocysts shed by infected felids become infectious upon sporulation and after successful entry into the body of the meat yielding animals; the pathogen transforms itself into tachyzoite, bradyzoites and then moves into the muscles and nervous tissues. Through this mechanism, the pathogen can effectively transmit the infection, if the infected meat is consumed by the humans [1–5].

Although, the *T. gondii* infections are widely prevalent in human beings, its prevalence rate is not uniform worldwide. It is observed that the infection rates are higher in Central and South America and continental Europe (50%–80%), while Alaska has the lowest prevalence rate of 1%. In the United Kingdom alone, more than 0.35 million people are infected with the parasite each year. However, the accurate estimates of the physical and economic burden of the disease could not be measured because of the limited data available on the overall incidence and severity of symptoms [6–11].

This review is aimed to discuss the current status and prevalence of toxoplasmosis, and also to consider the use of different medicinal plants as therapeutic agents for toxoplasmosis.

2. Clinical effects of toxoplasmosis

In healthy individuals, toxoplasmosis is generally asymptomatic because of effective immunity; however, the symptoms may be severe and prove fatal in immunocompromised individuals, such as those suffering from AIDS. Infected patients may experience fever or cervical lymphadenopathy, sometimes associated with myalgia, asthenia, or other nonspecific clinical signs. The clinical signs may persist for several weeks, mimicking infectious mononucleosis, especially since monocytosis can be observed on blood smears. Although, *T. gondii* is known to cause a subclinical infection, a primary infection during pregnancy may prove fatal and can induce abortions in human [12,13]. The infection during gestation may result in congenital toxoplasmosis characterized by chorioretinitis, hydrocephalus, deafness, and impaired mental development [14]. The parasite is also known to be associated with psychiatric disorders affecting behavior, personality and other phenotypic traits [15]. The risk of infection transmission from mother to the fetus is 30%–45%; of

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these, majority are sub-clinical infections (60%) but 30% of them may suffer from hydrocephalus, intracerebral calcification, chorioretinitis and mental retardation. A significant number (9%) results in death of the fetus [16]. Degree of damage to the fetus depends on the gestational age, and the greatest risk of congenital toxoplasmosis occurs during the early period of pregnancy. Whereas the highest level of transmission occurs during the third trimester of the pregnancy and may cause an enlarged uterus, but fetal injuries are usually much less severe during this period [17]. The incidence and consequences of congenital toxoplasmosis are so severe that, in Austria and France, it is mandated by law to test seropositivity for *T. gondii* in all pregnant women on their first visit to the gynecologist [18]. It is worthwhile to claim that even an acute infection can result in devastating disease in the fetus, AIDS patients, recipients of organ transplant and patients receiving anti-cancer therapy [19–22].

T. gondii is one of the parasites, which has got broad host ranges, the very high prevalence rate in humans, including pregnant women and immune-compromised patients. The transmission of *T. gondii* usually occurs by drinking contaminated water (oocysts from a feline source), ingesting of infective oocysts contaminating food product, venereal and congenital transmission, colostrum and also by ingesting of contaminated milk [23]. Toxoplasmosis is found to be more common in rural areas, which might be due to the higher contact of human body with animals like sheep, goats and cattle either in-house or farms or by eating unwashed fruits and vegetables, which might be contaminated with cat feces [18,24].

3. Treatment for toxoplasmosis

An ideal anti-*Toxoplasma* drug should have parasiticidal properties against different stages of the parasitic life cycle, including penetration into cysts. It should show effective penetration through the placental barrier to reach the main sites of fetal infection and should be free from fetal toxicity and teratogenicity. However, none of the currently used drugs fulfilled these criteria. Sulfadiazine and pyrimethamine are the two drugs used as a part of standard therapy for toxoplasmosis and are particularly beneficial when the parasite actively multiplies during the acute stage of the disease. In chronic conditions, drugs like diaminodiphinylsulfone, atovaquone, spiramicyne, and clindamycine are used, but these drugs have limited efficacy due to the emergence of resistant strains and their toxicity to the fetus during pregnancy. Drugs, such as sulfadiazine (sulfonamide) have significantly lower parasiticidal activity if it is not used along with pyrimethamine (dihydrofolate reductase inhibitor) [25,26].

If pyrimethamine is used for treatment of *T. gondii* infection, it results in the suppression of bone marrow function and can cause neutropenia. Furthermore, these drug results in folate depletion that can have detrimental effect on the early fetal development and therefore, this treatment cannot be used in congenital toxoplasmosis during the first trimester of pregnancy. The combination of sulfadiazine and pyrimethamine also increases the risk of kidney stones, allergy and other forms of hepatic or renal complications [27]. Although, new drugs such as atovaquone, epiroprim (DHFR inhibitor) and fluoroquinolone antibiotics are effective *in vitro* and *in vivo* against *T. gondii*, their usage in pregnancy is limited as their safety has not been established [25]. There is, therefore, a definite need for development of more viable treatment options to prevent toxoplasmosis.

4. Anti-parasitic medicinal plants: history and success

Humans have been using herbal plants for centuries to treat various infections with or without knowing their actual properties. Parasites are responsible probably for more than (1–2) billion infections, which cause several million deaths every year. Medicinal plant extracts usually contain complex mixtures consisting of several classes of secondary metabolites. Quite a large number of plants have been identified and researched, which produce natural products with significant anti-parasitic action [28]. It is out of scope of this review to mention and discuss all the medicinal plants individually that have been tested for some sort of anti-parasitic activity.

Traditional medicinal plant extracts have been proven to have anti-malarial effect. A species of plant *Cinchona officinalis* from the family of Rubiaceae was one of the first drug that was used to treat malaria in Central and South America. Plant such as *Cinchona officinalis* and *Artemisia annua* L. (Asteracea) were the basis of the development of anti-malarial drugs, including atovaquone (*Tabebuia* spp. of family Bignoniaceae) [29]. *Curcuma* plant species (Zingiberaceae) have been reported to show anti-parasitic activity against *Trypanosoma* [30,31]. Plants like *Baccharis retusa* (Asteraceae) and *Kalanchoe pinnata* (Crassulaceae) were screened and reported to exhibit anti-leishamanial activity [32]. Researchers have tried analyzing natural products against *Trichomonas* species as some of the strains have become resistant to the standard drugs [33]. A study conducted in India reported *Streblus asper* (Moraceae) to have anti-filarial activity both *in vitro* and *in vivo* [34]. Ascaridole, which is extracted from *Chenopodium ambrosioides* (Amaranthaceae) was found to be effective for hookworm infection [35]. The biological effect of diverse medicinal plants used to treat various parasitic infections, including the plant name, parts used and extraction method is tabulated below (Table 1).

Parasites are usually eukaryotes that share most of the biochemical and molecular properties with their eukaryotic host which makes it difficult to find an anti-parasitic drug. So this limitation has always to be kept in mind when we discuss a medicinal plant against parasitic infections. Several parasites have become resistant to standard chemotherapy; consequently medicinal plants can be an alternative choice. Strikingly, there is no sufficient data available regarding the anti-parasitic activity of medicinal plant extracts for many of the parasitic infections.

5. Medicinal plants and toxoplasmosis

All these aforementioned treatments are able to reduce or eliminate the clinical signs and symptoms but do not kill the parasite or cure the infected host. Hence, the improvement of safe and affordable drugs to eradicate this disease is of paramount importance, which requires extensive scrutiny of compounds having the ability to kill the parasite with least or no toxicity to humans. Recently, greater prominence has been given towards finding alternative medicine to deal with parasitic diseases and consequently, numbers of studies have been performed on the endless number of herbs belonging to a different

Table 1

Medicinal plants used for the treatment of various parasitic infections, including *T. gondii*.

Plant name	Parts used	Extraction method	Biological effect	References
Vernonia colorata	Stem and leaves	Air-dried, powdered and ethanolic extract	Anti-toxoplasmic activity	Benoit-Vical F *et al* [36]
Zingiber officinale	Stem and leaves	Air-dried, powdered and ethanolic extract	Anti-toxoplasmic activity	Choi KM *et al* [37]
Sophora flavescens	Stem and leaves	Air-dried, powdered and ethanolic extract	Anti-toxoplasmic activity	Choi KM *et al* [37] and Youn HJ [38]
Torilis japonica	Stem and leaves	Air-dried, powdered and ethanolic extract	Anti-toxoplasmic activity	Youn HJ [38]
Eurycoma longifolia	Roots	Air-dried, powdered and methanolic extract	Anti-toxoplasmic activity	Kavitha N *et al* [39]
Calotropis procera	Leaf	Air-dried, grounded and ethanolic soak	Anti-malarial effect (Compound CP1-04-61)	Mudi SY and Bukar A [41]
Pulicaria crispa	Leaf	Air-dried powdered and methanolic extract	Anti-cancer and anti-malarial activity and growth inhibition of wheat-rootlet activities	Gouda YG *et al* [42] and Sathiyamoorthy P *et al* [52]
Euphorbia retusa	Leaf and stems	Dried at room temperature, powdered and methanolic extract	Anti-bacterial activity	Refahy LAG [43]
Rumex spinosa	Leaf	Air-dried methanolic extract Air-dried chloroformic extract	Anti-fungal (*Candida Albicans*) Anti-fungal (*Alternaria alternata* and *Saccharomyces cerevisiae*)	Mandeel Q and Taha A [44]
Ochradenus baccatus	Leaves and flower	Air-dried powdered and methanolic extract	Anti-malarial, Anti-leishmanial, Anti-trypanosomal and hypocholesterolemic effect	Mothana RA *et al* [45]
Lycium shawii	Leaves	Oven-dried, grounded and methanolic extract	Hypoglycemic, antiplasmodial and antitrypanosomal effect	Alkuwari AD *et al* [46]
Commiphora Molmol (*Myrrh*)	Stem and leaf (oleo-gum resin)	Air-dried ethanolic extract	Anti-toxoplasmic activity	Al-Zanbagi NA [47,48]
Curcuma longa	Stem and leaf	Air-dried, water and ethanolic extracts	Anti-toxoplasmic activity	Al-Zanbagi NA [49,50]
Juniperus procera	Stem and leaf	Air-dried ethanolic extract	Anti-toxoplasmic activity	Al-Zanbagi NA [51]

ethnobotanical origin. The pharmaceutical industry has been successful in developing drugs from natural products to treat a number of parasitic diseases. Over the past five decades, medicinal plants are being screened systematically to explore their potential anti-parasitic properties [36–39].

The flora of Saudi Arabia has a rich biodiversity comprising some of the most valuable medicinal plants around the world. Some of the medicinal plants are known to possess antimicrobial, anti-protozoan, immuno-stimulant activities and used by the traditional healers to cure a series of infections. *Calotropis procera*, commonly known as giant milkweed used to treat leprosy, elephantiasis fever, menorrhagia, malaria and snake bite in the traditional medicine, is reported to exhibit significant antimalarial activity against *Plasmodium falciparum* [40,41].

Pulicaria crispa, a perennial bushy desert plant used to treat inflammation and as an insect repellent is reported to exhibit anti-tumor and anti-malarial activity. In addition to the cytotoxic activity, the plant extracts have been reported to be active against *Leishmania* and some fish bacterial pathogens [42]. Many species of *Euphorbia* have been reported to possess antitumor, antiproliferative, antimicrobial, antipyretic, analgesic and molluscicidal activity due to the large variety of compounds, including diterpenes, tannins, alkaloid, triterpenes and flavonoids. *Euphorbia retusa* grown in the wild in Saudi Arabia is stated to retain significant antimicrobial activity [43].

Rumex spinosa commonly known as a devil's thorn is an annual herbaceous plant known as Hambaz. The methanolic leaf extract is recorded to display significant inhibitory activity against *Candida albicans*, while the chloroform extract exhibited significant inhibitory activity against *Alternaria alternata* and *Saccharomyces cerevisiae* [44]. *Ochradenus baccatus* is one of the highly valued medicinal plants in Saudi Arabia owing to its hypocholesterolemic and anti-malaria properties. The methanol extract of the plant is found to be active against *Plasmodium*, *Leishmania* and *Trypanosoma* with significantly low IC_{50} values establishing its antiprotozoal efficacy *in vitro* [45]. In Saudi Arabia, *Lycium shawii* commonly known as 'Gul Gaider' is used for the treatment of diabetes and hypertension by traditional practitioners. Scientific studies have demonstrated that *Lycium shawii* extract possesses hypoglycemic, antiplasmodial and antitrypanosomal activity [46].

In a continued effort to improve the efficacy of the therapies against *T. gondii*, researchers have evaluated the anti-*Toxoplasma* effects of numerous medicinal plant extracts both *in vitro* and *in vivo*. According to a study done in Western Africa, it was reported that aqueous extracts of *Vernonia colorata* exhibited significant anti-*Toxoplasma* activity with an IC_{50} of 16.3 mg/L. The organic solvents, such as dichloromethane, acetone and ethanol also exhibited a ten-fold gain in activity with IC_{50} values as low as 1.7, 2.6 and 2.9 mg/L, respectively. Both the infusion and decoction of *Vernonia colorata* extracts exhibited a similar pattern of activity, which showed a marked inhibition for concentrations >10 mg/L and total inhibition at concentrations >30 mg/L [27]. Choi *et al* evaluated the anti-*Toxoplasma* activity of methanolic extracts of 15 traditional medicines used to treat *T. gondii* infections. Of these extracts, significant anti-*Toxoplasma* activity was observed with *Zingiber officinale* (EC_{50} = 0.18 mg/mL) and *Sophora flavescens* extracts (EC_{50} = 0.20 mg/mL) [37].

Ethanol extracts of *Torilis japonica* and *Sophora flavescens* were found to inhibit *T. gondii* proliferation by 99.3% and 98.7%, respectively at a concentration of 156 ng/mL *in vitro* [29]. Two active fractions of *Eurycoma longifolia* root extracts, namely TAF355 and TAF401, are reported to possess significant anti-*Toxoplasma* activity with IC_{50} values of 1.125 μg/mL and 1.375 μg/mL, respectively [39].

In Saudi Arabia literature search showed that only five studies have been undertaken to evaluate the anti-*Toxoplasma* activity of medicinal plants. Al-Zanbagi reported that Oleo-gum resin of *Commiphora molmol* used for the treatment of bronchitis and in wound healing was evaluated for the anti-*Toxoplasma* activity in mice. It was observed that treatment with 100 and 200 mg/kg/d of the resin reduced the mean number of tachyzoites by 96.6% and 100.0%, respectively [47,48]. Similarly, in a murine model, the alcohol extracts of *Curcuma longa* were found to exhibit significant anti-*Toxoplasma* activity as evidenced by 98.6% and 99.2% growth inhibition of *Toxoplasma* tachyzoites at 100 and 200 mg/kg/d dose, respectively [49,50]. In another study, administration of water extracts of *Juniperus procera* fruits, leaves and stems (400 mg/kg/d) exhibited a growth inhibition of tachyzoites by 53.5%, 50.0% and 48.0%, respectively in mice [51].

6. Concluding remarks and perspectives

Many of the medicinal plants exhibit anti-*Toxoplasma* effects and have been used by ethnic communities around the world as a therapeutic agent for combating toxoplasmosis. Medicinal plants contribute as sources for the production of new medicines and may enhance the effects of conventional anti-microbials, which will probably decrease costs and improve the treatment quality with less-side effects. Continued efforts are needed to exploit the current medicinal plants, which exhibited anti-*Toxoplasma* effects, search for new medicinal plants, and make them the more accessible alternative to the standard drug therapies.

Conflict of interest statement

We declare that we have no conflict of interest.

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