**A Brief Insight on Anti-Toxoplasma Gondii Activity of Some Medicinal Plants**

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**Abstract**

The treatment of *Toxoplasma gondii* (*T. gondii*) infection accentuates the problem of the limited effectiveness of the available anti-parasitic agents and their side effects and also, the potential appearance of resistant *Toxoplasma* strains. Thus, the search of the newer and more effective drugs is needed. This study aimed to review the efficacy of some herbal plants extracts on *T. gondii* infection, in an attempt to overcome the side effects of hazardous drugs. It was found that many herbal plants extracts exhibit anti-*Toxoplasma* activity including *Nigella sativa*, *Zingiber officinale*, *Myrrh*, *Piper nigrum*, *Capsicum frutescens*, *Curcuma longa*, *Azadirachta indica* (neem) and *Melia azedarach*. However, their efficacies in human toxoplasmosis remain to be confirmed in clinical trials. The use of such medicinal plants extracts has a more beneficial effect in prophylaxis as well as treatment of this protozoan infection through being safer, acceptable, affordable, culturally compatible, widely available at low cost and suitable for treatment of chronic toxoplasmosis.

**Keywords**: *Toxoplasma gondii*; Treatment; Sulfadiazine; Pyrimethamine; Medicinal plants

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**Introduction**

Toxoplasmosis caused by the ubiquitous obligatory intracellular coccidian protozoan, *Toxoplasma gondii* [1] that has many forms. There are three infectious stages of *T. gondii*: tachyzoites (rapidly multiplying form), bradyzoites (tissue cyst form), and sporozoites (in oocysts). Tachyzoites [Figure 1A] are found in the acute phase of the disease and are responsible for clinical manifestations. They are susceptible to the immune response of the host and to drug action. Cysts [Figure 1B] are the resistant form of the parasite, persisting for the host's entire life. Cyst walls are resistant to both drugs and the immune system [2].

**Figure 1:**

A. *T. gondii* tachyzoites from the peritoneal exudates of infected mice stained with Giemsa

From: http://www.eyecalcs.com/DWAN/pages/v4/v4c046.html
B. Tissue cyst of *T. gondii* in brain smears of mouse stained with Giemsa

http://jjmicrobiol.com/?page=article&article_id=3964

*T. gondii* has a wide range of hosts including humans, mammals, birds and marine mammals. About one third of the human population has been exposed to this parasite. Humans or animals can acquire *T. gondii* infection post-natally by ingestion of undercooked or raw meat from infected animals, or ingestion of food or water contaminated with oocysts excreted by infected cats [3]. The population structure of *T. gondii* consists of three main clonal lineages; Type I (including RH, a highly virulent strain), Type II (including avirulent strains like Me49 and PRU), and Type III (including avirulent strains like NED) correlated with virulence expression in mice [4].

The treatment of toxoplasmosis is essential as *T. gondii* causes serious morbidity and mortality in pregnant women and in immunocompromised patients who are suffering from the Acquired Immune Deficiency Syndrome (AIDS) or those undergoing chemotherapy. There are still few effective treatments for this disease, their main goal being the reduction of the parasite replication rate to avoid more extensive damage to the organs involved as well as to prevent the severe complications. It is therefore clear that anti-Toxoplasmic therapy need to be effective against all strains of *T. gondii*, be capable of killing tachyzoites and have a high ocular and cerebral penetration. However, their side effects, the potential appearance of resistant strains and the lack of efficacy against the tissue cyst of the parasite are particular drawback of the available treatments. Therefore, additional studies involving the parasite’s proteomics and functional genomics are necessary for the development of new and safer drugs, a viable and safe vaccine [5].

Previous studies demonstrated that, in the absence of a vaccine, and with growing parasite resistance to therapeutic drugs, natural products can be effective against intracellular parasites such as *Plasmodium falciparum*, *Leishmania amazonensis* and *Trypanosoma cruzi* [6, 7, 8]. Natural products play a highly significant role in the process of developing new drugs in the areas of cancer and infectious diseases [9], with over 60 and 75% of the used drugs deriving from plant extracts, respectively [10]. The medicinal value of these plants lies in some chemical substances that produce a definite physiological action on the human body. The most important of these bioactive constituents of plants are alkaloids, tannins, flavonoids and phenolic compounds [11, 12].

**Pathogenesis of *T. gondii* infection**

During natural infections, *Toxoplasma* initially crosses the intestinal epithelium, actively enter the blood stream, and cross non-permissive biological sites such as the blood–brain-barrier, the blood–retina barrier and the placenta [13]. *Toxoplasma* invades numerous organs, infecting a broad spectrum of cell types [14]. The first step of cell invasion by *T. gondii* is recognition of an attachment point. The two special organelles involved in this invasion process, rhoptries and micronemes, each discharging proteins during the process [15]. Following the rapid cellular invasion the parasite resides within a vacuole, derived primarily from the host cell’s plasma membrane [16]. *T. gondii* asexually multiplies and cause cellular disruption, leading to cell death. The resulting necrosis attracts inflammatory host cells, such as lymphocytes and monocytes. This inflammatory response causes the major pathology in infected individuals. As host resistance develops, usually around three weeks post infection, tissue cysts may form in many organs, primarily in the brain and muscles. These quiescent cysts enable *T. gondii* to evade the adaptive host immune. As tissue cysts periodically rupture, the released bradyzoites are killed by the host immune system. If immune surveillance becomes compromised due to chemotherapy or AIDS, these bradyzoites develop into tachyzoites, causing active toxoplasmosis [14].

*T. gondii* infection in immune-competent individuals is rarely symptomatic, but toxoplasmosis occurred in fetus and immunocompromised hosts may result in a severe disease or
even lethal damage [17]. The immune response to *T. gondii* infection is individual and complex [18]. *T. gondii* triggers an innate immune response characterized by a rapid recruitment of neutrophils to the site of infection, followed by a strong Th1 protective response associated with the production of proinflammatory cytokines, including interleukin-12 (IL-12) and tumor necrosis factor-α (TNF-α) [19]. Although cell-mediated immunity plays the major role in resistance against *T. gondii*, humoral immunity is also involved in controlling the parasite [20].

*T. gondii* affects the retina and the underlying choroid, causing retinochoroiditis; the most common cause of posterior uveitis (intraocular inflammatory syndrome) in immunocompetent patients [21]. Toxoplasmic retinochoroiditis may occur either immediately or long after the initial infection or in reactivation [22, 23]. Recurrent attacks of toxoplasmic retinochoroiditis might result from rupture of dormant cysts in the retina and release viable parasites that induce necrosis and inflammation or hypersensitivity reaction to parasite antigen [24]. Moreover, it was found that *T. gondii* infection induced DNA damage in retinal cells [25].

There is an increasing attention towards the role of adhesion molecules in the pathogenesis and immune responses to parasitic infections. Intercellular Adhesion Molecule-1 (ICAM-1) has been implicated in the pathogenesis of many diseases including toxoplasmosis [21, 26]. Elevated production of ICAM-1 by *T. gondii*-infected resident cells may initiate local immune reactivity during primary infections and during recurrent reactivation episodes in *Toxoplasma*-induced retinochoroiditis [27].

**Synthetic anti-Toxoplasmal drugs**

An ideal drug for treatment of toxoplasmosis would show effective penetration and concentration in the placenta, transplacental passage, parasiticidal properties against the different parasitic stages, penetration into cysts, distribution in the main sites of fetal infection and a total lack of fetal toxicity and teratogenic effects. No available drug fulfills all these criteria. A sulfonamide alone, such as sulfadiazine, lacks parasiticidal activity when it is not used in combination with pyrimethamine [28, 29]. The combination of pyrimethamine and sulfadiazine remains the mainstay for treatment and prophylaxis of most clinical presentations of toxoplasmosis. These drugs have a synergistic action by inhibiting *T. gondii* folic acid synthesis, which is essential for parasite survival and replication [30]. Pyrimethamine interferes with replication of the parasite as it inhibits the enzyme Dihydrofolate Reductase (DHFR) a key enzyme in the synthesis of purines [29] while, sulfadiazine acts as a competitive antagonist for Para-Aminobenzoic Acid (PABA), one of the precursors of folate production [31]. In fact, prompt treatment may achieve rapid resolution, minimize inflammatory damage, prevent widespread tissue destruction and decrease the chances of the parasite dissemination [25].

However, this combination has shown efficacy against acute toxoplasmosis [32] but failed against chronic cerebral toxoplasmosis [33]. Treatment of chronic toxoplasmosis is hampered by the poor drug brain penetration to achieve therapeutic concentrations resulting in the failure to eliminate the encysted form of the parasite. Furthermore, the treatment of patients with AIDS suffering from toxoplasmic encephalitis with the combination of pyrimethamine with sulfonamides is associated with frequent and severe adverse reactions [34] and entails a significant mortality rate, usually associated with relapse after withdrawal of therapy for reasons of toxicity, mainly because of the sulfonamide component of the combination. The high frequency of sulfonamide-induced toxicity in AIDS patients often makes completion of a full course of therapy difficult [35, 36].

Several treatment failures of toxoplasmic encephalitis, chorioretinitis, and congenital toxoplasmosis have been reported [30, 37-39]. Doliwa et al., [30] found three *T. gondii* strains naturally resistant to sulfadiazine and developed *in vitro* two sulfadiazine resistant strains, RH-R<sup>S</sup>DZ and ME-49-R<sup>S</sup>DZ, by gradual pressure. In addition, the prolonged use of these drugs may cause hematologic and renal toxicity [40] and the potential
to contribute to clinical failure by selecting drug-resistant parasite variants.

The current use of pyrimethamine for treatment of *T. gondii* infection is associated with suppression of bone marrow and can result in neutropenia even when accompanied by leucovorin supplements. Furthermore, this treatment is not used to treat congenital toxoplasmosis in the first trimester of gestation when folaite depletion can have additional detrimental consequences for early fetal development. Moreover, the combination of pyrimethamine with sulfadiazine can give rise to further concern due to allergy, kidney stones, or hepatic or renal complications [41].

Taking into account all these difficulties, some alternative therapies were developed and some drug combinations are available to replace the classical therapeutic model. In this context, an alternative therapy is the combination of clindamycin and pyrimethamine, which has an efficacy similar to that of the combination with sulfadiazine, and which is also associated with various side effects [42]. Furthermore, they were found to be genetically polymorphic and associated with more severe manifestations of disease. An association of great interest is the one between trimethoprim and sulfamethoxazole. Known as cotrimoxazole, its active compounds act synergistically, inhibiting two consecutive steps of folinic acid biosynthesis in a manner similar to that observed for pyrimethamine-sulfadoxine. Cotrimoxazole is well tolerated and less toxic to hematopoiesis. AIDS patients taking cotrimoxazole show a high incidence of adverse effects, and its use is discouraged in pregnant women because it crosses the placental barrier [43]. Other combination treatments include atovaquone and clindamycin, which are effective during the acute infection [44, 45] and reduced the severity of toxoplasmonic encephalitis relapses [46]. However, low bioavailability, lack of brain penetration, and incipient resistance [47] hamper the full therapeutic potential of this combination.

Another treatment option is spiramycin, a macrolide antibiotic, which is effective against acute toxoplasmosis, less toxic than other drugs, and able to achieve high concentrations in the placenta [48]. The anti-toxoplastic activity of spiramycin was evaluated in murine models of infection using a type-1 (RH) or type-2 (Me 49) strain of *T. gondii*. In mice infected with 2x10² tachyzoites of the RH strain, treatment with spiramycin at 100 and 200 mg/ kg/day had only a limited effect, despite some dependent prolongation of survival; it was unable to protect mice against death [49]. However, spiramycin demonstrates poor penetration across the blood brain barrier and does not reach effective concentrations in the brain due to the presence of the efflux transporters multidrug-resistant protein 2 (Mrp2) and P-glycoprotein, for which spiramycin is a substrate [50,51].

Among the other possible therapies, the antitoxoplasmic activities of tetracyclines have been studied in animal models. The results of those studies with tetracycline, doxycycline, chlorotetracycline, terramycin, and dimethylchlortetracycline have led to disparate conclusions on the activity of these drugs, with some studies finding activity and others finding no activity [52]. Dihydrofolate Reductase (DHFR) inhibitors such as epiroprim and antibiotics such as fluoroquinolones are effective *in vitro* and *in vivo* against *T. gondii*. However, they cannot be used in pregnant women because their potential harmful effects on the embryo or fetus have not been properly examined [28].

The discovery of viable low-toxicity compounds capable of preventing and treating *T. gondii* would represent a great advance in the treatment of infections in immunocompromised patients [53]. Several substances obtained from plants have been studied for the antiparasitic activity against *T. gondii*, and many of these compounds have proven to be more effective than the currently used therapy.

**Effect of some medicinal plants on *T. gondii***

Nowadays, there is an increasing awareness of the therapeutic potential of natural products and medicinal plants that are frequently considered to be less toxic and free from side effects than synthetic drugs in treating various diseases. The importance of these plants as sources of natural product bioactive molecules to medicine lies not only in their
pharmacological or chemotherapeutic effect, but also in their role as template molecules for the production of new drug substances [54].

Medicinal plants as Myrrh [55], Piper nigrum, Capsicum frutescens, Curcuma longa [56], Nigella sativa [57], Zingiber officinale [58], Azadirachta indica (neem) and Melia azedarach [59] have proven to be anti-toxoplasmal effects than the currently used therapy. From this point of view, this study aimed to review the efficacy of these herbal plants extracts on T. gondii infection in comparison to the commonly used drugs.

Nigella sativa [Figure 2], commonly known as black seed or black cumin, has been known to include many pharmacological effects including anti-inflammatory, immuno-potentiating effects, antihelminthic and antiprotozoal activities [57, 60]. It has been shown to enhance the T cell mediated immune response [61] by increasing in the ratio of helper to suppressor T cells and enhancing natural killer cell activity in healthy volunteers [62]. Rayan et al., [57] recorded the anti-Toxoplasma activity of Black Seed Oil (BSO) in induced murine infection with the Me49 parasite strain. It was found that the BSO treatment significantly increased survival and decreased brain cyst burden compared with the infected untreated control. The anti-Toxoplasma action exhibited by BSO may be attributed to the presence of different classes of alkaloids and phenolics [63, 64] that are known for their antiprotozoal activity [65] and also, it may have been a result of the immunomodulatory properties of BSO. Several studies point to the effect of black seed and thymoquinone (the main active constituent of the volatile oil extracted from the seeds) on the immune system by modulating the levels of pro- and anti-inflammatory mediators [66]. Furthermore, thymoquinone was found to reduce the nitric oxide production in supernatants of lipopolysaccharide stimulated macrophages, without affecting their cell viability [67]. Protection against T. gondii infection requires the prompt development and persistence of an active type-1 cytokine response characterized by the production of inflammatory cytokines, IFN-γ and TNF-α [68]. Nigella sativa was found to enhance the production of these cytokines [61].

Pro-inflammatory cytokines at infection site are important for recruitment and activation of leukocytes, which mediate local host defenses [69]. Although the inflammatory reaction induced by pro-inflammatory cytokines during T. gondii infection is crucial for control of the parasite, a critical immunoregulation is required to prevent host immunopathology [70].

Zingiber officinale [Figure 3], ginger, has been used in folk medicine as a medicinal plant, as well as a spice and food in many countries. Numerous experimental and clinical trials have proven ginger for its range of therapeutic activities such as antibacterial, antiparasitic, antidiabetic, antiemetic, hypolipidaemic and hepatoprotective properties [71]. Choi et al. [58] evaluated the antiparasitic effect of Ginger root Extract (GE) and GE/F1 (fraction 1 obtained from GE) against T. gondii in vitro and in vivo. They demonstrated that GE/F1 not only induces anti-T. gondii effects causing the inactivation of apoptotic proteins in infected host cells through the direct inhibition of T. gondii but also has antiparasitic properties which inhibit inflammatory cytokine secretion in vivo. The versatile biological activities of ginger are attributed to its phytochemical constituents like gingerol, zingerone and zingiberol [71].
Regarding *Azadirachta indica* (neem) [Figure 4] and *Melia azedarach* (cinnamon), their leaves have been reported to exhibit immunomodulatory, anti-inflammatory, antihyperglycemic, anticarcinogenic, nematicidal, antiparasitic, antiviral, insecticidal and antioxidant properties. There are over 50 different bioactive compounds (terpenoids and others) of the neem and cinnamon extracts, but their major components are limonoids such as Azadirachtins (AZ) that responsible for their different activities [72, 73]. Melo et al., [59] performed in vitro assays with cinnamon and neem aqueous extracts against the intracellular development of *T. gondii* tachyzoites. These extracts were capable of interfering with and eliminating the intracellular development of *T. gondii*. After treatment with neem and cinnamon for 24 h, the percentage of infected cells and the number of intracellular parasites drastically decreased. The reduction in the number of intracellular parasites is related to the accentuated and progressive morphologic disorganisation of tachyzoites within parasitophorous vacuole. During the incubation of the extracts, progressive morphological and ultrastructure alterations led to intense vesiculation and complete elimination of the parasite from the intracellular medium. At the same time, no morphological effects were observed in the structure of the host cell. The general biological action of these extracts is the induction of lipid peroxidation, generation of antiproliferative and antioxidant effects and detoxication of enzymes [74, 75]. *T. gondii* has a high lipid concentration in plasma and intraparasite membranes, including organelle content [76]. The integrity of the secretory system of *T. gondii* is vital to its invasion, survival and development. Melo et al., [59] showed that the secretory system of the parasite suffered drastic disorganisation and vesiculation, possibly because of the action of the chemical components of the extracts on their highly lipidic membranes.
host for *T. gondii*. They demonstrated that TAF 355 and TAF 401 effectively inhibited the growth of *T. gondii*, and was less toxic to Vero cells than clindamycin. With regard to the mechanism of action for TAF 355 and TAF 401 against *T. gondii*, it may be attributed to the anti-oxidant properties of *E. longifolia*, which have been well documented in the previous studies [80]. It is known that the mitochondria are the largest source of reactive oxygen species within cells [81]. Uncontrolled superoxide flashes in mitochondria contribute to global oxidative stress, playing a key role in hypoxia/reoxygenation injury in cells [82]. This model provided a rational explanation for why TAF 355 and TAF 401 inhibited *T. gondii* growth and protected the Vero cells by selective toxicity.

*Dictamnus dasycarpus* is known to have many medicinal properties, including anti-inflammatory, anti-fever, and anti-rheumatic activities. Ethanolic extracts of *Dictamnus dasycarpus* were tested *in vitro* and *in vivo* for their anti-*T. gondii* activity and cytotoxicity as compared with that of sulfadiazine. The selectivity of *Dictamnus dasycarpus* extract showed anti-*T. gondii* effects higher than that of sulfadiazine in *in vitro* testing. However in *in vivo* animal test, the inhibition rate of *Dictamnus dasycarpus* extract was similar to that of sulfadiazine [83]. This indicates that *Dictamnus dasycarpus* extract may be a source of new anti-*T. gondii* compounds.

*Tinospora crispa* Miers (family Menispermaceae) was used to treat malaria [84], filariasis [85] and also well known for anti-inflammatory, antispasmodic properties [86]. *Psidium guajava* L. (from family *Myrtaceae*) has been employed for treating various diseases such as relieving cough, pulmonary disorders, wounds, and ulcers. Its fruits have tonic, cooling, laxative, and anti-helmintic activities [87]. In a study carried by Lee et al., [88], crude methanolic extract from *T.crispa* stem and crude aqueous extract from *P. guajava* leaves were investigated in their respective crude alkaloids content, potential cytotoxicity activity and anti-*T. gondii* effect *in vitro*. Both crude plant extracts contained high amount of crude alkaloids and were not toxic to Vero cells. Following non-toxicity finding of the extracts, the *in vitro* anti-parasitic assay was carried out with clindamycin served as the positive control. *T. crispa* stem crude extract with EC50 value of 7.71 ± 1.56 μg/mL, showed potential anti-*T. gondii* activity as the results were comparable to clindamycin (EC50 = 6.24 ± 0.53 μg/mL). These findings suggested that the selective alkaloids in the *T. crispa* stem fractions may be the key factor for their anti-toxoplasmic activity.

The antitoxoplasmic activity of spiramycin and Myrrh [Figure 5] were evaluated in murine models of intraperitoneal infection using the RH strain of *T. gondii*. Myrrh treatment significantly enhanced protection and decreased the tachyzoites number in the peritoneal fluid of experimented mice, 4 days after infection. With the treatment of 100 and 200 mg/kg/day of Myrrh the percentage of growth inhibitions were 96.6%, 100% respectively, as that of the reference drug, spiramycin (% growth inhibitions were 96.6%, 75.9% correspondingly) compared by the control infected untreated mice [55]. These results were comparable to that recorded by Mui et al., [41] who observed that Triazine was highly effective against *T. gondii* tachyzoites both *in vitro* and *in vivo*. The administration of Triazine intraperitoneally reduced the mean number of RH strain tachyzoites present in peritoneal fluid substantially 4 days after intraperitoneal infection of mice with 10,000 tachyzoites.

**Figure 5:** Myrrh
A) Plant From: http://patty-patcards.blogspot.com/2012/04/general_07.html
B) Gum From: http://www.dhealthstore.com/myrrh-essential-oil-egyptian-1oz.html
Nutmeg (*Myristica fragrans* Houttuyn) [Figure 6] is the seed kernel of inside the fruit and mace is the lacy covering (aril) on the kernel. By using nutmeg essential oil, it exhibited strong anti-*T. gondii* activity with low cytotoxic effects against normal cell line. This anti-Toxoplastic activity may attribute to its potential active compounds against *T.gondii* parasite such as myristicin, limonene, eugenol and terpinen-4-ol [89]. In addition, the medicinal plant *Juniperus procera* was tested by using fruit, leaves and stems extracts as a growth inhibitor for *Toxoplasma* tachyzoites in dose of 400 mg/kg/day [90]. It was found that the percentage of growth inhibition of the fruit, leaves and stems of *Juniperus procera* was 53.5, 50 and 48 % at concentration of 4: 1 respectively.

The anti-toxoplasmic activity of water and ethanol extracts as well as the oil of some home spices (*Piper nigrum, Capsicum frutescens, Cinnamomum cassia* and *Curcuma longa*), were evaluated in murine models of intraperitoneal infection using the RH strain of *T. gondii*. Female mice were infected with 2x10^2 tachyzoites / ml, and then treated intraperitoneally with the home spices at 100 and 200 mg/kg/day for seven days. The tested extracts reduced the mean number of tachyzoites present in the peritoneal fluid of the experimental mice. The most effective extract was *Curcuma longa* [Figure 7] ethanol extract which showed a 98.6% and 99.2% inhibition of the growth of *Toxoplasma* tachyzoites in 100 and 200 doses respectively compared to the control infected untreated mice [56]. The anti-toxoplasmic effect of *Curcuma longa* may be attributed to the curcumin which is the main bioactive component of turmeric exhibits a great variety of pharmacological activities including anti-protozoal [91, 92]. The cytotoxic effect of curcumin on the parasite may result from damage of both its mitochondrial and nuclear DNA [6]. In addition, curcumin inhibited the parasite growth and adherent capacity, induced morphological alterations, deformation due to swelling and cell agglutination, and provoked apoptosis-like changes as observed on a study carried by El-Sayed et al., [92] in the amoebicidal activity of *Curcuma Longa* against *Acanthamoeba castellanii* cyst. It has been reported that curcumin treatment had modulated cellular and humoral immune responses of infected mice leading to a significant reduction of parasite burden and liver pathology in acute murine schistosomiasis mansoni [93].

Additionally, alcohol extracts of the herbs *Sophora flavescens, Sinomenium acutum, Pulsatilla koreana, Ulmus macrocarpa* and *Torilis japonica* were studied in vitro as anti-protozoal activity against cultures of *T. gondii* and *Neospora caninum*. These extracts were serially diluted to final concentrations ranging from 625 to 19.5 ng /ml in media and added to wells containing either *T. gondii* or *Neospora caninum* tachyzoites in equine dermal cells. The inhibition of the growth of parasite was measured using ^3^H-uracil incorporation as compared to untreated controls. *Torilis japonica* inhibited *T. gondii*
proliferation by 99.3, 95.5, 73.0 and 54.0% in the range from 156 to 19.5 ng/ml, and *Sophora flavescens* inhibited *T. gondii* proliferation by 98.7, 83.0 and 27.2% in the range from 156 to 39 ng/ml [94].

**Conclusion**

This study concluded that medicinal plants may prove to be a useful agent for the treatment of toxoplasmic infections both *in vitro* and *in vivo*. Therefore, the clinical trials to test the safety and value of these plants in the prophylaxis and/or treatment of toxoplasmic infections especially in immunocompromised patients will be needed.

**References**


