# Overview about Oxidative stress in Toxoplasmosis

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## Abstract

The protozoon parasite was named Toxoplasma gondii based on its morphology: "toxo" for arc- form; "plasma" for life and "gondii" for the host where it was first found. Although a single species has been described for the genus Toxoplasma, there are several clonal lineages that differ in their pathogenicity and virulence. The primary mechanism of the host's defence against protozoan infection is oxidative stress (OS). Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the antioxidant system of the organism. ROS include all highly reactive and unstable derivatives of molecular oxygen, such as hydrogen peroxide (H2O2), superoxide anion (-O2) and the most dangerous hydroxyl radical (HO). The characteristic action of ROS is the degradation of polyunsaturated fatty acids in the process termed lipid peroxidation, which leads to the production of harmful molecules, including malondialdehyde (MDA). T. gondii is one of many intracellular infections that can be killed by ROS which are produced during an immune response. It was discovered that ROS can stop T. gondii from growing in infected animals' monocytes. For instance, high H2O2 concentrations may prevent tachyzoites from proliferating intracellularly. Superoxide dismutases (SODs) (one cytosolic and two mitochondrial), catalase (CAT), and three peroxiredoxins, including one 1-Cys peroxiredoxin and two 2-Cys peroxiredoxins, are all expressed by toxoplasma cells.

**Keywords:** Oxidative stress, Toxoplasmosis

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## Introduction

*Toxoplasma gondii* was discovered by both **Nicolle** and **Manceaux** in 1908 in the lymphatics and liver of *Ctenodactylus gondii* (the North African rodent) and in rabbits in Brazil (**Ferguson, 2009)**. The protozoon parasite was named *Toxoplasma gondii* based on its morphology: "toxo" for arc-form; "plasma" for life and "*gondii"* for the host where it was first found **(Weiss and Dubey, 2009)**.

The parasite is infecting broad range of warm- blooded animals including one third of world human population **(Montoya and Liesenfeld,2004)**. The pathogenic potential of *Toxplasma gondii* was recognized in 1920s and 1930s **(Weiss and Dubey, 2009).**

*T. gondii* is a globally distributed protozoan parasite which can infect about 30 to 50% of human populations. In Europe more than one million of the reported annual cases are contracting infection through drinking oocyst-contaminated water or ingestion of tissue cyst-contaminated food, primarily raw or undercooked pork and lamb **(WHO, 2015).**

Prevalence in USA and United Kingdom ranges from 8 to 22% **(Jones *et al,* 2014)**. In USA, toxoplasmosis was the fourth cause of hospitalization after salmonellosis, campylobacteriosis and Norovirus infections **(Scallan *et al,* 2011)**.

In Central America, South America, and continental Europe, estimates of infection range from 30 to 90% **(Minbaeva *et al,* 2013).** In both developing and developed countries, the parasite infects approximately 30-50% of the human population **(Flegr *et al,* 2014)**.

The highest seroprevalence of *T. gondii* has been reported from developing countries like Ethiopia. For example, the seroprevalence of T. gondii recorded in northern Ethiopia was 76.5% **(Muluye *et al.,* 2013).**

The consumption of contaminated food is the main source of infection, including meat products and dairy products. Recently, contamination has been detected in fresh products with oocysts and marine products. Despite the great health problems that are caused by *T. gondii*, currently there are no standardized methods for its detection in the food industry **(Marín-García *et al.*,2022).**

Although, contaminated food is considered the main route of infection in humans, it has been reported that up to 50% of infections are caused by food transmission using a novel multiplex Polymerase Chain reaction (PCR) assay **(Shapiro *et al.,* 2019)**. **Luna *et al.*,2019,** informed the presence of *T. gondii* in meat, water, cucumber, and guava juice, both inert and living surfaces in school dining rooms of Colombia.

The concern about this zoonosis and its transmission has been increasing. In 2018, the EFSA recommended a serological screening of livestock to identify positive farms **(Shapiro *et al.,* 2019)**. In the following year, The European Food Safety Authority (EFSA) report found that food-borne transmission accounts for 40–60% of *T. gondii* infections **(EFSA and ECDC, 2019)**.

Reports from Iran showed that chronic toxoplasmosis was a risk factor for type 2 diabetes mellitus **(Colli *et al.,* 2010)**, however, there was no statistical relationship between serum levels of anti-*T. gondii* antibodies and the risk for diabetes mellitus **(Khalili *et al.,* 2018).** In fact, the reason for high seroprevalence of *T. gondii* infection among diabetic patients and the mechanism by which toxoplasmosis relates to diabetes mellitus are not clearly defined **(Woyesa and Taylor-Robinson, 2021).**

On the other hand, there is a variation in seroprevelance between domestic animals and human. In a study conducted in China from 2000 to 2017, toxoplasmic infection was about four times more likely to occur in domestic animals than in humans (23.4% versus 8.2%) **(Dong *et al.,* 2018).** A similar study conducted in seven Chinese regions reported high seroprevalence of *T. gondii* among meat-producing animals, with pigs, chickens and cattle having a 24, 20 and 9.5% rate of infection, respectively **(Deng *et al.,* 2018)**. Also, it was found that frequent contact with domestic cats was independent predictor to acquire *T. gondii* infection **(Wilking *et al.,* 2016).**

**Hamed *et al.* (2018)** detected a significant seroprevalence of toxoplasmosis in mentally retarded children attending Abu Reesh Hospital of Cairo University. Therefore, screening for toxoplasmosis during pregnancy is important especially when mothers are exposed to risk factors such as contact with cats and consumption of undercooked meat.

Furthermore, the same researchers conducted a study to evaluate the seroprevalence of *T. gondii* infection in diabetic patients. They found that the seropositivity for anti-*Toxoplasma* antibodies in diabetic patients was found to be higher than that in non-diabetic patients.

Interestingly,the seroprevalence of *T. gondii* of cats was reported to be 97% in Egypt **(Al-Kappany *et al,* 2011)**.Moreover, **Khattab et al., 2019** revealed a seroprevelance of 45.0 and 5.0% in type 1 diabetic patients by anti-IgG and anti-IgM.

**Oxidative stress in Toxoplasmosis:**

The primary mechanism of the host's defence against protozoan infection is oxidative stress (OS) **(Delavari *et al.,* 2017).** Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the antioxidant system of the organism **(Betteridge, 2000).**

ROS include all highly reactive and unstable derivatives of molecular oxygen, such as hydrogen peroxide (H2O2), superoxide anion (-$O_2$) and the most dangerous hydroxyl radical (HO) **(Halliwell, 2012).**

ROS homeostasis is closely related to many other reactive molecules, such as reactive carbonyl species (RCS) and reactive nitrogen species (RNS) **(Lushchak,2014).**

Since ROS are produced as a consequence of oxygen metabolism, it is impossible to avoid them in aerobic organisms. They are generated in the cytosol and in such organelles, such as mitochondria and peroxisomes **(Szewczyk-Gole *et al.*,2021).**

ROS play a role in cell signalling activities at physiological levels, but increased oxidative stress brought on by excessive ROS production may damage all cellular macromolecules, including lipids, proteins, and nucleic acids, ultimately resulting in cell death **(Dincel and Atmaca, 2016).**

The characteristic action of ROS is the degradation of polyunsaturated fatty acids in the process termed lipid peroxidation, which leads to the production of harmful molecules, including malondialdehyde (MDA) **(Del Rio *et al.*,2005).**

MDA is a highly reactive aldehyde that harms tissues by oxidation. MDA is a significant thiobarbituric acid reactive compound (TBARS) in the organism and is a member of the TBARS class. Therefore, the TBARS measurement is frequently employed to determine the MDA concentration **(Dalle-Donne *et al.*,2006).**

TBARS and MDA are considered the significant indicators of oxidative stress and lipid peroxidation in biological samples **(Rahal *et al.,* 2014).**

Oxidative stress plays a significant role during *Toxoplasma* infection in the host and the parasite **(Van De Crommenacker *et al.*,2011)**

Cellular disruption and cell death occur as a consequence of *T. gondii's* asexual reproduction in an infected host. Lymphocytes and other inflammatory host cells are drawn to the necrosis that results. Huge levels of ROS and RNS are produced during the immune response against the parasite **(Çinar, 2015).**

Oxidative stress resulting from the host response is toxic to parasites **(Zhuang *et al.*,2020)**. Moreover, it is crucial in the development of toxoplasmosis in both animals and humans **(Karaman *et al.*,2008).**

**Antioxidant Defense of *Toxoplasma gondii:***

*T. gondii* is one of many intracellular infections that can be killed by ROS which are produced during an immune response. It was discovered that ROS can stop *T. gondii* from growing in infected animals' monocytes. For instance, high H2O2 concentrations may prevent tachyzoites from proliferating intracellularly **(Xue *et al.*,2017)**. Consequently, the parasite needs to defend itself from the host's forced oxidative burst **(Charvat and Arrizabalaga, 2016).** Superoxide dismutases (SODs) (one cytosolic and two mitochondrial), catalase (CAT), and three peroxiredoxins, including one 1-Cys peroxiredoxin and two 2-Cys peroxiredoxins, are all

expressed by toxoplasma cells **(Akerman and Müller, 2005).**

The main antioxidants involved in the protection against oxidative stress and oxidative metabolic byproducts include SODs and CAT **(Ding *et al.*,2000)** SODs are metalloproteins that help break down superoxide anions into molecules of oxygen and peroxide **(Scandalios, 1993).**

Hydrogen peroxide is converted by CAT to water and oxygen, which lowers its cellular level **(Charvat and Arrizabalaga, 2016).** CAT's cytosolic location and inherent kinetic characteristics imply that this enzyme may be best adapted for the defence against oxidative stress in host cells **(kwok *et al.*,2003).** CAT appears to have a significant role in invasion and replication inside the parasitophorous vacuoles, according to knockout studies **(Bosch *et al.*,2015).** *T. gondii* without CAT showed decreased virulence in mice and greater vulnerability to exogenous hydrogen peroxide **(kwok *et al*.,2003).**

**Oxidative Stress in the Early Stages of the Acute Phase of Toxoplasmosis:**

During the acute phase of toxoplasmosis, ROS are extensively produced, and oxidative stress is created in the tissues of infected animals. As the host's defense against the infection even in the absence of symptoms, *T. gondii* seropositive cats exhibit elevated ROS levels **(Faria *et al.*,2018).** Phagocytosis is a common component of the host immune response to infections, which occurs after lymphokines have activated mononuclear phagocytes **(Dahlgren and Karlsson, 1999).**

Although practically all mammalian tissues contain the NADPH-oxidase complex (Nox), which generates ROS, phagocytes have a more prominent role in the production of ROS in the host's defence against infections **(Bedard and Krause, 2007).** As a result, host phagocytes are the primary site where parasiticidal processes are activated via ROS production. As a factor controlling the intracellular survival of *T. gondii* parasites within macrophages, Nox-mediated ROS production **(Matta *et al.*,2018).**

Additionally, nitric oxide (NO) produced by macrophages was found to have an antiparasitic effect on protozoa **(Szewczyk-Gole *et al.*,2021).** According to **Tonin *et al.* (2015)**, an increase in NO levels was found in goats with toxoplasmosis. *T. gondii* infection is linked to an elevated NO level, which is produced to manage the infection. Tachyzoites of both virulent and non-virulent strains can be directly killed by NO or stimulated to produce the heat-shock protein 70, which aids in their transition to the bradyzoite stage and cyst formation **(Szewczyk-Gole *et al.*,2021).**

**Oxidative Stress in the Later Stages of the Acute Phase of Toxoplasmosis:**

The oxidant–antioxidant balance in the later stages of the acute phase of *T. gondii* infection showed increased SOD and glutathione S-transferase (GST) activities 30 days after infection in the brain, liver and kidney of rats. This suggests that the increased antioxidant defense persisting later on in the acute phase can be used to diagnose *T. gondii* infection and may be helpful, especially in cases where the diagnosis of *T. gondii* infection is difficult in the earlier stage of the acute phase **(Türko ˘glu *et al.*, 2018).**

**Oxidative damage in the host during *Toxoplasma* infection:**

In addition to being effective against *T. gondii*, the rapid release of ROS and NO also adds to oxidative stress, which causes tissue damage and the pathophysiology of the disease **(Alajmi *et al.*,2019).** Damage to the intracellular lysosomal membrane caused by oxidative stress is followed by apoptosis or necrosis **(Terman *et al.*,2006).**

Increased lipid peroxidation is linked to decreased function of the defence system preventing tissue damage from free radicals in *Toxoplasma* seropositive people and animals **(Al-Azzauy, 2011).** It was reported that gerbils infected with *T. gondii* exhibit increased lipid peroxidation **(Szewczyk-Gole *et al.*,2021).** In addition, **Delavari *et al.* (2017)** found that rats infected with *T.*

*gondii* had higher levels of MDA in their liver cells, blood serum, and testes **(Nazarlu *et al.*,2020).**

Humans with chronic toxoplasmosis have significantly higher MDA concentrations in their serum, according to some studies **(Szewczyk-Gole *et al.*,2021).** When compared to healthy persons, the MDA levels in *Toxoplasma* seropositive patients who were asymptomatic were considerably greater **(Al-Kuraishy et al., 2020).** There was no relationship between the MDA concentration and either gender or age **(Al-Azzauy, 2011).**

**The antioxidant compounds**

**1-Resveratrol:**

Resveratrol (trans-3,4′ ,5-trihydroxystilbene, RSV), is a small polyphenol found in many plants, especially mulberries, peanuts, and grapes **(Kulkarni and Canto, 2015)**.

RSV has a wide range of pharmacological activities, including anti-cancer **(Ko *et al.*, 2017)**, anti-oxidant **(Xia *et al.*, 2017)**, anti-inflammatory **(de S´ a Coutinho *et al.*, 2018)**, and anti-*T. gondii* **(Contreras *et al.*, 2021).**

It helps in reducing inflammation along with oxidative stress that contributes to prolonging the lifespan of organisms belonging to different species **(Szkudelska *et al.*,2020).**

**Antioxidant effect of Resveratrol:**

It has a double effect that can increase the activity of antioxidant enzymes and can act as a free radical cleanser **(Izzo *et al.*,2021). Samsamikor *et al.*,2016** reported that 500 mg/day RV supplementation, significantly increased serum SOD and total antioxidative capacity, and decreased serum MDA concentrations**.** In addition, it has been shown that RSV can maintain antioxidants levels for biological activities **(Zhang *et al.*,2021)**.

RSV increase the concentration of some antioxidant enzymes like glutathione peroxidase (GPx), glutathione S-transferase and glutathione reductase **(Garcia-Martinez *et al.*, 2021),** and can effectively inhibit iNOS production **(Zhang *et al.*,2021)**.

RSV can attenuate the activation of immune cells and the subsequent synthesis and release of proinflammatory mediators **(Meng *et al.*,2008).** Previous studies indicate that RSV treatment modulates cytokine profiles and attenuates inflammatory process caused by *T.gondii* infection**(Bottari *et a.*, 2018).**

Regarding the antiparasitic activity, RSV possess parasiticidal efficacy against *Leishmania amazonensis* and *Trypanosoma cruzi*. In *Leishmania amazonensis* RSV exhibited both anti-promastigote and anti-amastigote effects, increased the percentage of promastigotes, reduced the mitochondrial potential and decreased the activity of the arginase enzyme in macrophages that lead to elimination of parasites (**Ferreira et al.,2014)**. RSV showed strong anti-parasitic effects against *Trypanosoma cruzi* via promoted metacyclogenesis, reduced epimastigotes growth, blocked differentiation and/or replication of intracellular amastigotes **(Campo,2017).**

**2-Herbal plants:**

- ***Lepidium sativum* seed extract (LSSE):**

*Lepidium sativum* is a popular herb that commonly known as (Hab el Rashaad or Thufa). It is grown in many regions in Saudi Arabia such as Hijaz, Al-Qaseem and the Eastern province **(Gilani *et al.*, 2013).**

It is frequently used in Saudi traditional medicine, as well as in many African countries for the treatment of gut disorders like diarrhea among other medicinal uses,while in the Western world its leaves are used in salads **(Azaizeh *et al.*,2006).**

Phytochemical studies of *Lepidium sativum* seeds have revealed the presence of tannins, benzyl isothiocyanate, flavonoids, alkaloids, triterpenes and sterols, which are known to have antioxidant, anti-inflammatory, analgesic andanti-parasitic activities **(Raish *et al.*, 2016).**

Interstenigly, *Lepidium sativum* is an antiparasitic with documented efficacy against *Eimeria tenella* **(Adamu and Boonkaewwan, 2014),** and *Echinococcous granulosus* **(Bahrami *et al.*, 2016),** in addition, **Abuelenain *et al.*,2021** revealed the anti *Trichinella* activity of *Lepidium sativum*, it resulted in a significant reduction in adult worm numbers and in muscle larvae count.

It was found that *lepidium sativum* seed extract improved leukopenia associated with lymphocytopenia which induced by trypanosome infection **(Al-Otaibi *et al.*, 2018).** There is significant correlation between LSSE role in decreasing the oxidative stress markers and improvement of hematological parameters **(Raish *et al.*, 2016).**

**Eucalyptus extract:**

*Eucalyptus* is a large genus of Myrtaceae family, represented by 900 species and subspecies. It is native to Australia and can be found all around the world. Native Australians used Eucalyptus leaves for wound healing and treating fungal infections **(Gilles *et al.*, 2010).**

According to previous studies, *Eucalyptus* has beneficial biological effects such as, anti-microbial, anti-hyperglycemic, anti-oxidant activities and anti-trichomonas activity **(Youse *et al.*, 2012).**

*Eucalyptus* extracts contain polyphenols, terpenoid and cineol that had previously displayed remarkable antioxidant activity **(El-Moein et al., 2012).** It was found that eucalyptol which are the principal compounds of the essential oils of *Eucalyptus* species, exhibit antioxidant activity due to the presence of phenolic compounds **(Luís *et al.*, 2017).**

**Mirzaalizadeh *et al.*,2018** reported that *Eucalyptus* extract had *invivo* and *invitro* anti *Toxoplasma* activities additionally, it showed anti-oxidant effect and higher survival rates**.**

Olive (***Olea europaea***) extract:

The Olive (*Olea europaea L.*) is a small tree belonging to the family Oleaceae. It is native to tropical and warm temperate regions of the world, and it is one of the oldest known cultivated plants**(Boskou,1996).**

Olive leaves are considered as a cheap raw material which can be used as a useful source of high added value products such as phenolic compounds **(Briante *et al.*,2002)**. Main phenolic compounds in olive leaves extracts are oleuropein, hydroxytyrosol, verbascoside, apigenin-7-glucoside and luteolin-7-glucoside, **(Goldsmith *et al.*,2014)**

Olive leaves extract in several studies in animals and humans showed a high antioxidant capacity **(Soni *et al.*,2006)** and anti-inflammatory **( Khalatbary and Zarrinjoei, 2012)**

Maslinic acid(MA) (2R,3-dihydroxyolean-12-en-28-oic acid) is a triterpenoid compound related to oleanolic acid which is found in numerous plants **(Juan *et al.*,2006)** especially in considerable amount in fruit and leaves of *Oleaeuropaea* **(Lee *et al.*,2008).**

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* was previously evaluated **(De Pablos *et al.*,2010).** The authors observed alterations in gliding motility and ultra-structure in parasites treated with maslinic acid. Maslinic acid worked as other protease inhibitors that inhibit the growth and intracellular replications of *T. gondii and* blocks the entry of parasite into the cell as well. **(Jones *et al.*,2001)**

Intersentingly, it was found that olive leaf methanolic extracts has good efficacy and is a promising therapeutic agent against *Cryptosporidium*, diminishing the oocysts shedding, protecting the intestinal epithelial from deleterious effects of *C. parvum* **(Abd El-Hamed *et al.*, 2021).**

## Conclusion

Oxidative stress (OS) plays an essential role in the pathogenesis of common neurodegenerative diseases. We have previously shown that *Toxoplasma gondii* (*T. gondii*) induces high nitric oxide (NO) production, glial activation, and apoptosis that altogether cause severe neuropathology in toxoplasma encephalitis (TE). The objective of this study was to investigate the cytotoxic effect of OS and to identify a correlation between the causes of *T. gondii* induced neuropathology. Expression levels of glutathione reductase (GR), Cu/Zn superoxide dismutase (SOD1), neuron specific enolase (NSE), and 8-hydroxy-2'-deoxyguanosine (8-OHdG) were investigated. Results of the study revealed that the levels of GR ($P$ <0.005) and NSE ($P$ <0.001) expression in the brain tissue markedly increased while SOD1 activity decreased ($P$ <0.001) in the infected group compared to the non-infected group. In addition, intense staining for 8-OHdG ($P$ <0.05) was observed both in the nucleus and the cytoplasm of neurons and glial cells that underwent OS. These results were reasonable to suggest that *T. gondii*-mediated OS might play a pivotal role and a different type of role in the mechanism of neurodegeneration/neuropathology in the process of TE. The results also clearly indicated that increased levels of NO and apoptosis might contribute to OS-related pathogenesis of TE. As a result, OS and expression of NSE might give an idea of the disease progress and may have a critical diagnostic significance for patients with *T. gondii* infection.

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