

EFFICACY OF SOME DRUGS AND PATHOLOGICAL STUDIES ON TOXOPLASMA GONDII INFECTION IN MICE

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SUMMARY

The present investigation was conducted to study the effect of infection with *Toxoplasma gondii* and the efficacy of azithromycin and garlic tablets on treatment of acute murine toxoplasmosis in addition to study the histopathological changes due to infection. For this purpose, sixty Albino mice were used as experimental animals that equally divided into 6 groups. Estimation of survival rate, pathological studies, bioassay trial and immunofluorescent study were performed for each group of mice. High efficacy of azithromycin at a dose of 250 mg/kg/day on infected mice was shown, that increased survival rate (90% at the 7th day P.I) and decreased the histopathological changes when compared with control groups. Garlic

tablets at a dose of 500 mg/kg/day showed fewer efficacies in infected mice, survival rate (40% at the 6th and 7th day P.I) which was lesser than those groups treated with azithromycin. Pathologically, group treated with azithromycin showed improvement in histological pictures compared with group treated with garlic.

To identify the efficacy of the drug, at the end of the experiment, subinoculation of healthy mice by visceral and brain suspensions from surviving mice treated with azithromycin or garlic was performed as compared with subinoculation of suspension of brain and visceral of infected non treated mice inoculated into healthy mice, that showed death of these mice after three days post-infection (survival rate 0 %).

It was concluded that azithromycin has a significant effect in treatment of murine model toxoplasmosis, but it did not eradicate the parasite completely as few cysts remained in the brain, while garlic tablets had a limited effect for treating toxoplasmosis.

INTRODUCTION

Toxoplasma gondii: is a coccidian parasite of felids with human and other warm-blooded animals as alternative hosts (Degerli et al., 2003). Human infection generally occurs through the ingestion of raw or undercooked meat that contains tissue cyst of the parasite or through the ingestion of water or food contaminated with sporulated oocysts and congenitally through transplacental transmission from mother who acquired her infection during gestation (Abudullah et al., 1994). The organism recovered in tissue sections and body fluids have identical morphologic characteristic of tachyzoites, pseudocyst and bradyzoites but in cell cultures only tachyzoites are seen (Gutierrz., 1990). Experimental infections of animals with *Toxoplasma* were considered to be an important tool in the study of the effect of the parasitic invasion inside the animal body. Recently, many studies were carried out on experimental animals to evaluate the drugs effect in prophylaxis and treatment of toxoplasmosis. Some investigators searched

for safe and effective drugs to be used for the treatment of toxoplasmosis in pregnant women and infant. Mice were experimentally infected with *T. gondii* and the effects of these drugs were studied in vitro and in vivo to achieve the best results for application (Dagc and Aksuner, 2003).

The present study was carried out to give a spot light on the effect of some drugs used for the treatment of toxoplasmosis in murine models in addition to study histopathological changes due to infection.

MATERIAL AND METHODS

A - Material:

A-1. Experimental animals:

1) 90 Albino mice 4-5 weeks old, of 17-22 g weight and parasites-free were used as experimental animals; they were used for maintaining *Toxoplasma* strain, histopathological and immunofluorescent studies

B) Three rabbits about 1 kg weight were used for the preparation of polyclonal antiserum for immunofluorescent studies.

A-2. Preparation of *Toxoplasma* RH strain :

The maintenance of *Toxoplasma* strain :

This virulent strain was originally isolated from a cephalitic child in the USA by (Sabin, 1941). It is maintained by peritoneal inoculation of Swiss Albino mice. The

infected mice then was killed within three days post infection. Calculation of the parasites in one ml of peritoneal exudates was made by using improved neubour chamber. Healthy mice were regularly inoculated intraperitoneally with 1×10^4 organisms at a dose of 0.1 ml by tuberculin syringes to induce acute infection by *Toxoplasma* RH strain, this strain was also used to prepare hyperimmune serum (Conly et al., 1981).

A-3. Preparation of *Toxoplasma* antisera :

Toxoplasma rabbit antisera (primary polyclonal antibodies) were obtained according to Alan and Robin (1988) procedure for the immunofluorescent technique

B - Methods :

B-1. Experimental Design :

To study the effect of the acute *Toxoplasma* infection and the efficacy of azithromycin and garlic tablet on these albino mice, sixty mice were used for this purpose divided into 6 groups, each composed of 10 animals as follows:

- Group 1: Non infected, non treated mice (negative control).
- Group 2: Infected with 1×10^4 *Toxoplasma* tachyzoites, none treated mice (positive control).
- Group 3: Infected with 1×10^4 *Toxoplasma* tachyzoites and orally treated mice with azithromycin in a dose of 250 mg/kg/day for 3days. (Moshkani and Dalmi, 2000).

- Group 4: Non infected and orally treated mice with azithromycin in a dose of 250 mg/kg/day for 3days.

- Group 5: Infected with 1×10^4 *Toxoplasma* tachyzoites and orally treated with garlic tablets in a dose of 500 mg/kg/day for 7days.

- Group 6: Non-infected and orally treated with garlic tablets in a dose of 500 mg/kg/day for 7 (Khoshazaba et al., 2007).

The experiment extended for 10 days post-infection.

B- 2. Survival Rate:

It was calculated in each group according to the following ratio (Eid et al., 2004):

$$\text{Survival rate} = \frac{\text{No. of animal survived}}{\text{Total No. of animals}}$$

B- 3. Pathological Study:

Pathological studies, smears from peritoneal exudates were taken from all groups and stained with Giemsa to detect the presence of the parasite. Postmortem examination was performed and macropathological changes were recorded. Samples from brain, liver and spleen were preserved in 10% neutral buffer formalin then processed and embedded in paraffin , sections of 4-5micron thickness were obtain and stained for H&E, PAS stain and Prussian blue (Clayden, 1971 and Bancroft et al., 1994).

B- 4. Bioassay Trial:

Mice were dissected and subinoculation of brain and viscera suspension were made from infected non treated group immediately after death and from surviving mice that were treated with azithromycin into healthy mice at the end of the experiment (10 days).

The method includes removal of brains and viscera from the survived treated mice with azithromycin, suspended in PBS (pH = 7.2), then inoculated intraperitoneally at a dose of 0.1 ml into 6 healthy mice, brain and viscera of infected non treated mice were also suspended in PBS, pH = 7.2 then inoculated intraperitoneally at a dose of 0.1 ml into 6 healthy mice (McLeod et al., 1988).

Survival rate of each group was calculated according to a ratio mentioned above.

B- 5. Immunofluorescent Study :

Indirect immunofluorescent technique was carried out on paraffin embedded tissues sections from all groups (from the dead and survived mice till the end of the experimental period) to detect *Toxoplasma* antigen in the infected tissues according to Matossian (1977) procedure. To localize the binding of primary specific antibody with antigen in tissue section, conjugated antiserum with Fluorescein isothiocyanate was used.

RESULTS

1. Survival Rate :

As shown in table 1 and Fig. 1, it was found that azithromycin at a dose of 250 mg/ kg / day in group 3 (infected, treated mice) increased the survival rate as it was 100 % from the 1st to the 6th day post infection (PI) then it was gradually declined (90%,70%,50% and 20%, respectively) from the 7th to the 10th day PI as compared with group 2 (infected and non-treated group) which had a rate of 100% from the 1st to the 4th day PI then it was 0% after the 4th day. The survival rate of group 5 (infected mice treated with garlic) was 100% from the 1st to the 4th day PI then began to decline to reach 90, 40 and 0 % at the 5th, 6th and 7th as well as 8th days PI, respectively.

2. Pathological Findings :

Impression smears stained with Giemsa of peritoneal exudates of infected non treated mice showed aggregation of tachyzoites in exudates of these infected mice (Fig. 2).

The macropathological examination of group 2 (positive control), were represented by severe congestion and multiple petechial hemorrhages in most of internal organs specially brain, liver and spleen. Hemorrhages were recognized on the meningeal surface of cerebrum in all of these infected mice. Multiple irregular pale foci were observed on

the surface of the liver and also in cut section. While, the micropathological examination of group 3 (infected treated mice with azithromycin) showed mild to moderate congestion in the internal organs. Few pale areas were seen on the surface of the liver in two mice of this group. Other macropathological lesions were observed in group 5 (infected treated mice with garlic tablet) represented by severe congestion and haemorrhage in the internal organs.

Histopathological examination of Group 2 (infected non treated mice):

A- Brain:

The lesions in brain varies from small focal areas of necrosis and mononuclear cell infiltration, to large areas of necrosis and calcification. Occlusion of some blood vessels with thrombus formation other vessels showed vacuolation and hyalinization of their walls (Fig. 3a&b). Large number of macrophages laden with hemosidrin pigment were seen in most of the necrosed areas (Fig. 4a,b&c).

B- Liver:

Examination of the liver revealed that hepatic vessels were widely dilated and engorged with blood with perivascular inflammatory infiltration, multiple defined necrotic foci, associated with inflammatory cells infiltrates (Fig. 5a&b).

C- Spleen:

The spleen revealed marked depletion in number of lymphocytes (Fig. 5c) with hyperplasia of megakaryocytes, edoma and hemolysed blood.

Histopathological examination of Group 3 (infected and treated mice with azithromycin):

A-Brain:

The main microscopical lesions in brain revealed few focal areas of micronecrosis with inflammatory and glial cells infiltrations. Also, there was Toxoplasma cyst without inflammatory reaction (Fig. 6a).

B- Liver:

The liver revealed mild congestion of blood vessels with few areas of necrosis and polymorphonuclear cells aggregation (Fig. 6b).

C- Spleen:

The spleen showed lymphocytic hyperplasia in the splenic corpuscles. The splenic sinusoids were dilated and contained lymphocytes and monocytes .

Histopathological examination of group 4 (non-infected and received azithromycin) demonstrated: no marked histopathological changes in the internal organs

Histopathological examination of group 5 (infected and treated with garlic):

A- Brain:

The brain showed focal areas of necrosis with aggregation of inflammatory cells (mainly neutrophils) and glial cells (Fig. 7a). Focal areas of encephalomalacia were also seen.

B- Liver:

The liver revealed congestion of hepatic blood vessels and sinusoids with the presence of multiple scattered areas of haemorrhages. The hepatic parenchyma showed multiple foci of necrosis with infiltration of inflammatory cells. The hepatocytes exhibited variable degenerative changes (Fig. 7b).

C- Spleen:

The spleen revealed moderate hyperplasia of lymphocytes in the splenic corpuscles

3. Bioassay Trial Findings:

The bioassay trial findings revealed no symptoms of infection and no marked macropathological changes in the internal organs of the healthy mice received subinoculation of brain tissues and visceral suspension of the infected and treated group with azithromycin. The survival rate was 100% as compared with subinoculation of brain tissues and visceral suspension of infected non treated group into healthy mice, the inoculated mice were died at the end of

the third day post infection, and the survival rate was 0%.

Different macropathological changes were observed in this group including severe congestion and multiple petechial hemorrhages in most of internal organs.

4. Immuofluorescent Studies:

Toxoplasma antigen showed marked fluorescent reaction through the meninges and in the wall of blood vessels of brain in mice of group 2 (infected non treated mice), and less in brain tissues of group 3 (infected and treated with azithromycin)

The antigen of the parasite in the liver of group 2 showed fluorescent reaction within the liver parenchyma while, the reaction was less in liver of group 3.

Spleen of all groups showed antigen reaction, but it was higher in group 2. (Fig. 8a,b,c&d).

DISCUSSION.

Bao et al. (1994) studied the histopathological changes in mice experimentally infected with a virulent strain of Toxoplasma infection; they found that all infected mice had many changes all over the body specially liver. They decided that extensive lesion and diffuse necrosis of liver cells were the main cause for sudden death of the infected mice while acute and retrograde

degeneration in kidneys, lungs and brain were important factors leading to death of the mice.

Khan et al. (1999); Mui et al. (2005) and Zhang et al. (2006) tried to find a safe and effective drugs to be used in treatment of toxoplasmosis and evaluated the efficacy of these drugs on experimental animals.

Azithromycin is a very powerful antibiotic widely used for many conditions such as toxoplasmosis and other parasitic infection (Glade and Snider, 1990 and Degerli et al., 2003).

The present study was designed to use azithromycin in treatment of murine model toxoplasmosis compared with garlic tablets. Although azithromycin doubled the survival time of these treated infected mice compared with positive control group which died at the end of fourth day post infection but, it did not eradicate the infection completely from the brain and viscera of these experimental animals as tissue cyst was detected in brain sections of the infected, treated mice. The results indicated the presence of chronic infection which was in agreement with those documented by Moshkani and Dalimi (2000). In this respect Sadak et al. (1999) and Tabbara et al. (2005) studied the efficacy of azithromycin against experimental toxoplasmosis; they observed improvement of pathological changes of the infected organs with reduction of the tachyzoites counts and increase in the survival rate of treated mice.

Moshkani and Dalmi (2000) studied the efficacy of atovaquone alone or in combination with azithromycin against tissue cysts of toxoplasmosis and they suggested that these drugs together may be effective in removing of tissue cysts from infected tissue of mice.

Garlic (*Allium sativum*) was recognized since ancient Egyption (Colorni et al., 1998). Garlic has immune modulator effect on infected tissues with toxoplasmosis (Colorni et al., 1998 and Buchmann et al., 2003). The report of Kumar and Berwal (1998) described the ability of garlic to strengthen the body's natural defense against infection by activating phagocytes B-cells and T-cells, all three levels of the cellular immune system. It is a broad spectrum antibiotic that would kill a wide variety of bacteria, fungi and parasite.

The results of the present study found a little effect of garlic tablets in treatment of toxoplasmosis which was disagree with those of Khoshazaba et al. (2007) who found that garlic tablet when administrated to healthy mice inoculated with 1×10^6 *Toxoplasma* tachyzoites, the infection eradicated completely from brain, liver and spleen of these mice.

Colorni et al. (1998) documented that commercial powders have limited effects against toxoplasmosis, this is in agreement with the result of the present study which

might be due to the instability of allicin and prone to breakdown in a relatively short time (Ankri and Mirelman, 1999).

Macropathological examination of the present work in infected non treated mice showed severe congestion and multiple petechial hemorrhages in brain, liver and spleen which were in agreement with those found by Eid et al., (2004). Azithromycin reduced congestion and hemorrhage in most internal organs of mice which indicates infection recovery (Gutierrz, 1990). Histopathological studies evident marked improvement in the pathological changes treated with azithromycin, which was expressed in the presence of the foci of micronecrosis with infiltration of few inflammatory cells. Hyperplasia in the number of lymphocytes in the splenic corpuscles which could be attributed to the enhancement of cell mediated immunity also examination of the liver revealed improvement in the pathological picture as compared with the infected control group.

The multiple necrotic changes recognized in brain, liver and spleen in the infected non treated group were due to the intracellular growth of tachyzoites as mentioned by Shalaby et al. (1993).

McGavin et al. (2001) attributed necrotic changes in lymphocytes of infected non treated mice group that *Toxoplasma* have the ability to lyse the infected cells and causes tissue damage.

In the present study, the presence of microscopic nodules of cellular infiltrates in the brain tissue are the earliest reaction of *Toxoplasma* infection in the central nervous system which consist of aggregations of microglial cells (Gutierrz, 1990). The reasons for the presence of tissue cysts in the brain of treated mice with azithromycin were in agreement with Dubey (1998) who mentioned that his tissue cyst formation had occurred after the host has acquired immunity.

Cox et al. (2005) mentioned that by time of tissue cyst forming, the inflammation began to subside

Demonstration of *T.gondii* parasitic antigen in the present study by immunofluorescent techniques in tissues of infected untreated mice were in agreement with that recorded by Amin (1980) who observed presence of the organism in tissue sections of infected mice with *Toxoplasma* RH strain.

Table(1): The survival rate of mice according to each group parameter

Group parameter	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	8th day	9th day	10th day
Infected & non treated(G2)	10/10 100%	10/10 100%	10/10 100%	10/10 100%	0/10 0%	0/10 0%	0/10 0%	0/10 0%	0/10 0%	0/10 0%
Non Infected & non treated(G1)	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%
Infected treated with Azithromycin (G3)	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	9/10 90%	7/10 70%	5/10 50%	2/10 20%
Non Infected & treated with Azithromycin (G4)	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%
Infected & treated with garlic tablets (G5)	10/10 100%	10/10 100%	10/10 100%	10/10 100%	9/10 90%	4/10 40%	4/10 40%	0/10 0%	0/10 0%	0/10 0%
Non Infected & treated with garlic tablets (G6)	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%	10/10 100%

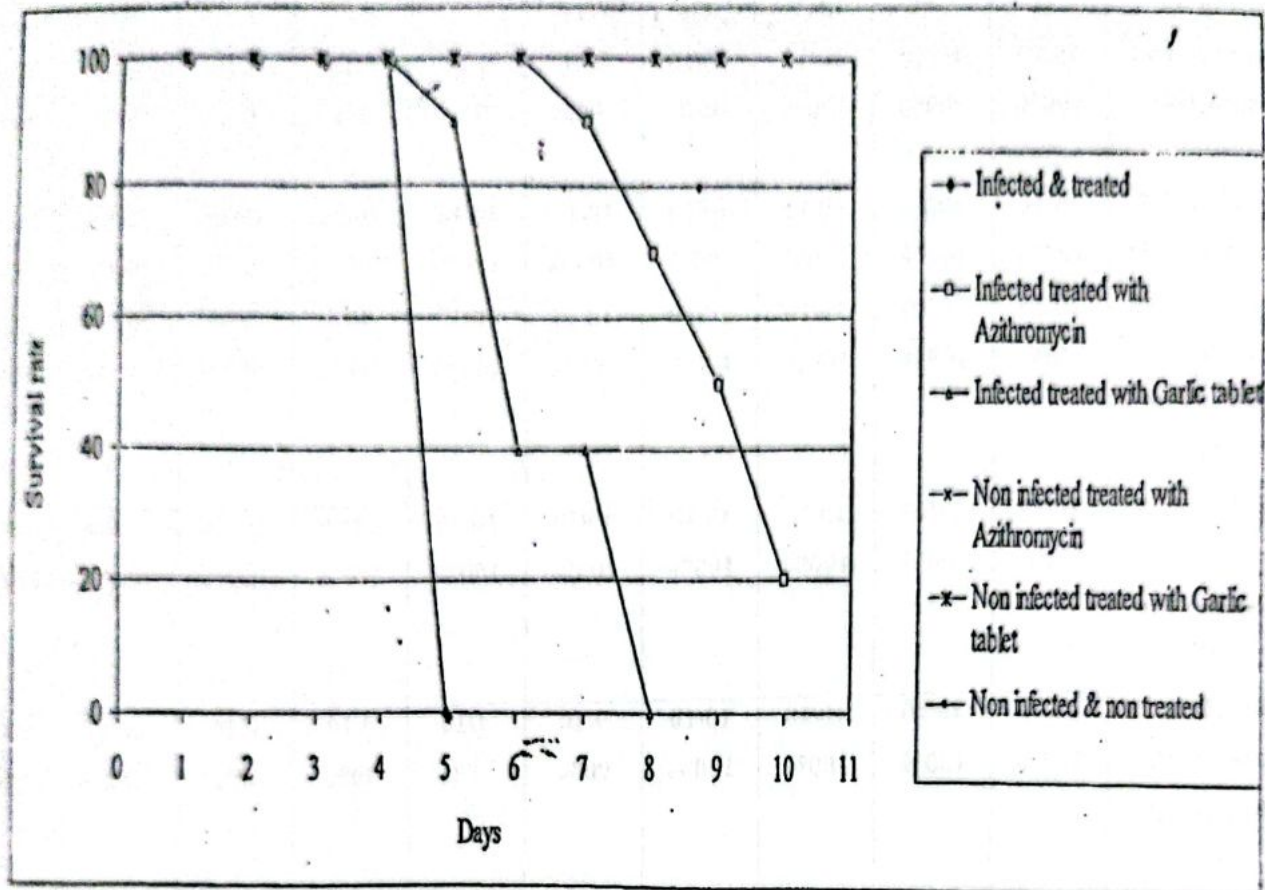


Fig. (1): Survival rate of mice according to each group parameter

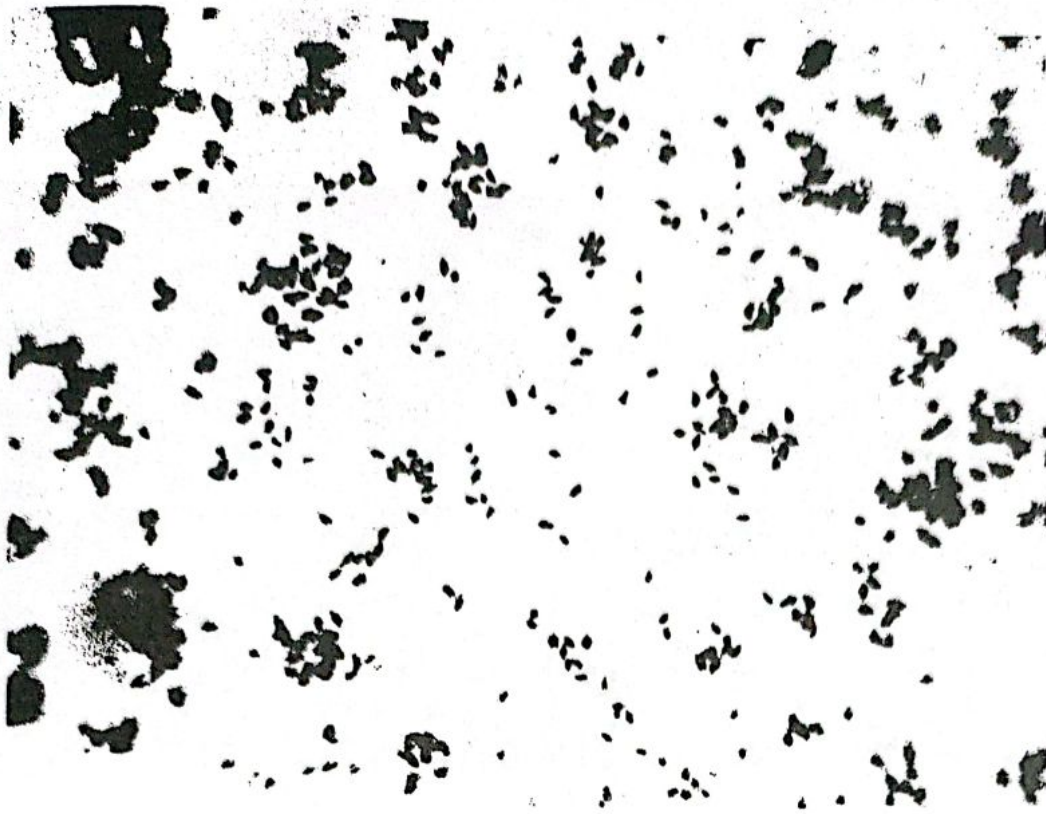


Fig. (2): Impression smears of peritoneal exudates of infected mice revealing *toxoplasma* tachyzoites (Giemas stain X 600).

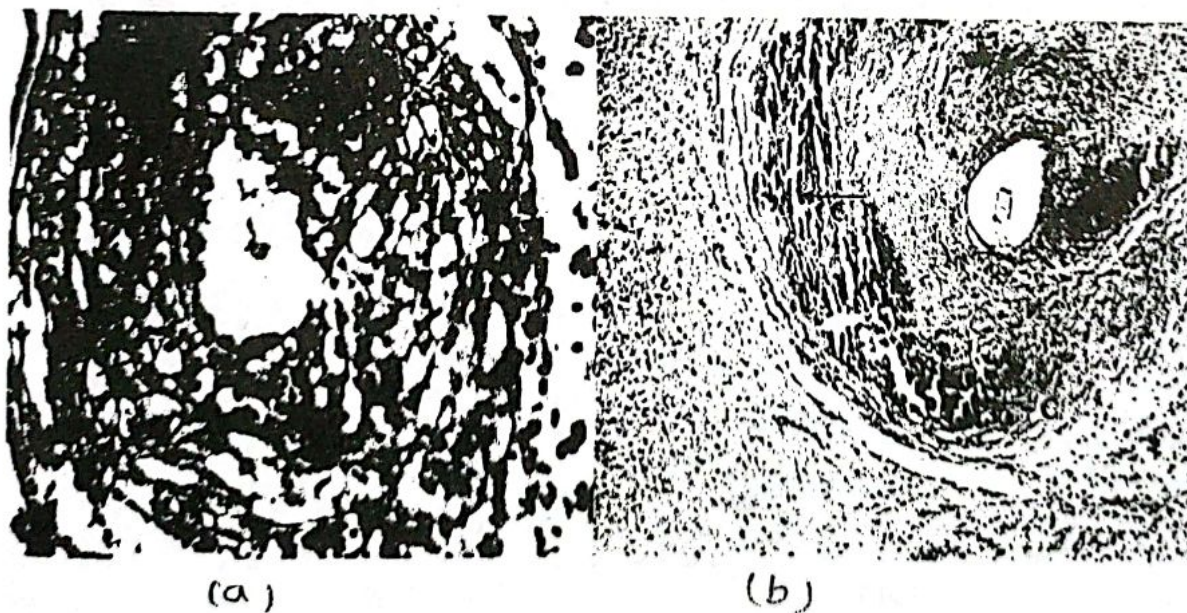


Fig. (3: a&b): a) Photomicrograph of brain of mice group 2 revealing vacuolation in tunica media, hyalinization in the wall of blood vessels and vasculitis. (H&E X 400). b) Photomicrograph from brain of group 2 demonstrating large focal area of necrosis and calcification. (H&E X 200).

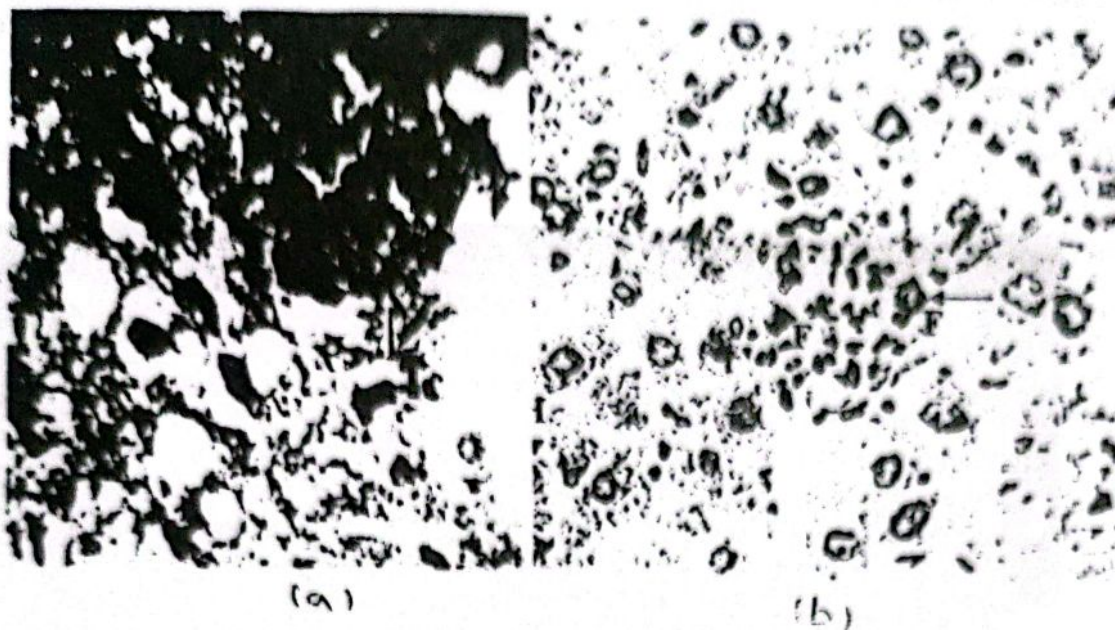


Fig. 6 a&b : a) Photomicrograph of brain of group3 showing *toxoplasma* tissue cyst. (PAS stain X 1000). b) Liver of group 3 revealing small focal area of necrosis with inflammatory cells aggregation. (H&E X 400).

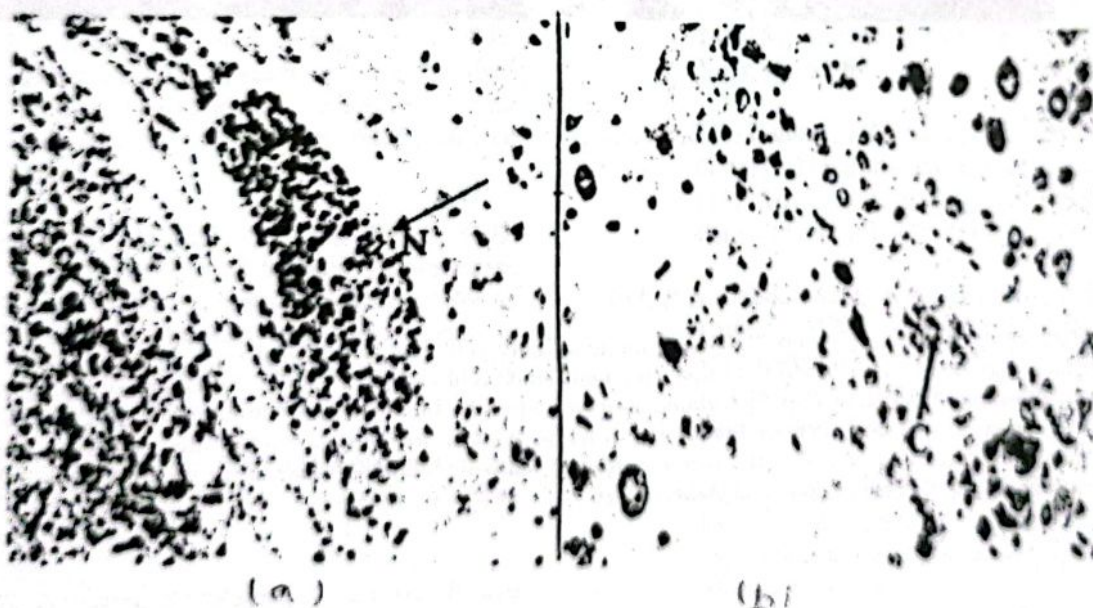


Fig. 7: a&b : a) Photomicrograph of brain of group 5 revealing focal area of necrosis with aggregation of inflammatory cells (H&E X 250). b) Liver of group 5 demonstrating congestion in blood vessels and sinusoids with haemorrhage. (H&E X 400).

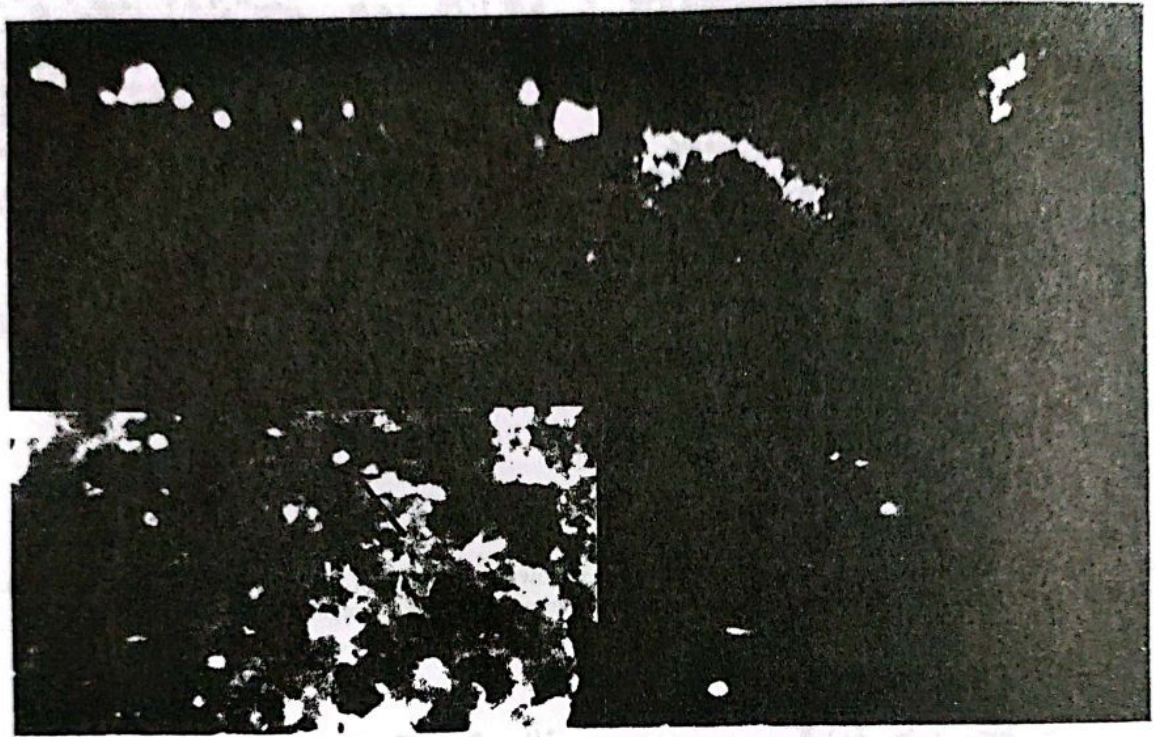


Fig. 8:a,b,c&d: a) Brain of group 2 showing immunofluorescent reaction against *toxoplasma* organism distributed throughout the meninges (Paraffin section, immunofluorescent stain X 400). b) Brain of group 2 showing immunofluorescent reaction against *toxoplasma* antigen within the blood vessels (Immunofluorescent stain X 400). c) Brain of group 3 revealing immunofluorescent reaction against *toxoplasma* tachyzoites within the brain tissue. (Immunofluorescent stain X 200). d) Liver of group 2 showing immunofluorescent reaction against *toxoplasma* tachyzoites antigen. (Immunofluorescent stain X 200).

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فاعلية بعض العقاقير ودراسات باثولوجية على العدوى بداء المقوسات في الفئران

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أجريت الدراسة الحالية لمعرفة تأثير العدوى بطفيلي داء المقوسات وفاعلية عقاري كل من الازثرومايسين وحبوب الثوم في علاج المرض الحاد في الفئران. استخدم لهذا الغرض ٦٠ فأرا ابيضاً تم تقسيمها الى ست مجاميع متساوية.

تم استخدام معايير كل من معدل البقاء ، تجارب القياس الحيوي وتفاعل التآلق المناعي لتقدير التأثير المعنوي للعقاقير موضوع الدراسة .

أوجدت الدراسة فاعلية عالية لعقار الازثرومايسين بجرعة ٢٥٠ ملغم/كغم/اليوم في الفئران المعدية بالطفيلي حيث اظهرت الدراسة ان معدل بقائها هو ٩٠% مقارنة بالفئران المعدية والمعالجة بحبوب الثوم بجرعة ٥٠٠ ملغم/كغم/اليوم والتي تبين انه اقل فاعلية في علاج الفئران المعدية حيث تبين ان معدل بقائها هو ٤٠%.

اظهرت الدراسة المرضية تحسن ملحوظ في الصور النسيجية للفئران المعدية والمعالجة بعقار الازثرومايسين مقارنة مع الصور النسيجية للفئران المعدية والمعالجة بحبوب الثوم.

تم في نهاية فترة التجربة دراسة كفاءة عقار الازثرومايسين والذي اظهر فاعليته في العلاج بعمل عدوى ثانوية بعالق ادمغة واحشاء الفئران المعالجة به والتي بقيت على قيد الحياة بفئران سليمة ومقارنتها بنتائج العدوى الثانوية بعالق ادمغة واحشاء الفئران المعدية غير المعالجة باي عقار بفئران سليمة حيث ماتت جميع فئران الثانية بعد 3 ايام من اجراء العدوى (معدل البقاء صفر%) بينما بقيت جميع حيوانات الاولى على قيد الحياة (معدل البقاء ١٠٠%).

تم الاستنتاج من هذه الدراسة ان لعقار الازثرومايسين تأثيراً معنوياً في علاج حيوانات التجارب المعدية بطفيلي داء المقوسات ولكنه (اي العقار) لم يمكننا من القضاء على الطفيلي بصورة كاملة ، حيث لوحظ وجود الاكياس النسيجية للطفيلي في ادمغة الحيوانات المعالجة به ، بينما اظهرت حبوب الثوم تأثيراً محدوداً في حيوانات التجارب التي تم معالجتها بها.