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Assessment of the Potential Effect of S-Methylcysteine Alone and in Combination with Metal-Organic Framework Nanoparticles on Experimental Toxoplasmosis in Immunosuppressed Mice

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Abstract

THIS STUDY was conducted to investigate the effect of S-methylcysteine (SMC) used singly, in combination with pyrimethamine (P) and sulfadiazine (S) regimen, and in conjugation with metal-organic framework nanoparticles (MOFs) on chronic toxoplasmosis in immunosuppressed mice. Fifty-four mice were immunosuppressed and divided into 9 groups (G); GI (negative control), GΠ (positive control), GⅢ- GⅣf (infected and treated); GⅢ (P-S), GⅣa (SMC50), GⅣb (SMC25), GⅣc (SMC25, P-S), GⅣd (SMC25-MOFs), GⅣe (SMC25, P-MOFs, and S-MOFs), and GⅣf (SMC25-MOFs, P-MOFs, and S-MOFs). The infected mice were orally inoculated with 20 *Toxoplasma* cysts/ mouse. Mice treatment stared Fifty days post infection for 10 consecutive days. Assessment of the therapeutic effect of each treatment model included: parasitological parameters (brain cyst burden), histopathological examination of mice brain sections, and immunological assessment of mice serum interferon gamma (IFN-Y) levels. GⅣf exhibited the highest percentage of brain cyst reduction (70.54%) and the highest percentage of IFN-Y levels increase (182.23%). Nevertheless, significant increase in glial cell number, an evident increase in the degree of inflammation. Drugs loaded on MOFs have anti-*Toxoplasma* effect on chronic toxoplasmosis in immunosuppressed mice.

Keywords: *T. gondii*, Pyrimethamine, Sulfadiazine, SMC, MOFs.

Introduction

Toxoplasma gondii (T. gondii) is an intracellular protozoan, that is responsible for toxoplasmosis [1]. In immunocompetent hosts, toxoplasmosis leads to mild symptoms. Nevertheless, in immunocompromised patients, reactivation of the underlying disease results in serious health problems [2]. Congenital toxoplasmosis is often a fatal or lifelong-disabling disease [3].

The production of interferon-gamma (IFN-γ) by the host immune cells in *T. gondii* infection occurs two to three days after the infection. IFN-γ lowers the quantity of parasites during the acute stage and keeps the parasite embedded as a bradyzoite in the tissue cysts during the chronic phase [2]. Diagnosis of toxoplasmosis relies mainly on serological tests [4].

The gold standard for the treatment is a synergistic combination of pyrimethamine and sulfadiazine. This combination acts on the folate biosynthesis pathway. However, failure rates and side effects of this combination are significant. Moreover, it does not affect tissue cysts, and it causes bone marrow suppression in the host. Therefore, folinic acid supplements are concurrently given for human cases [5]. Accordingly, alternative cheaper, safer, and more effective drugs are required.

Currently, the possible medicinal benefits of S-methylcysteine (SMC) are being studied by researchers. Garlic and onions are two examples of the many edible Allium plants that contain SMC, a

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hydrophilic cysteine-containing compound. It is among garlic's primary organosulfur compounds (OSCs) [6]. Garlic, SMC, and other OSCs of raw or extracted garlic have demonstrated antidiabetic, anti-inflammatory, antioxidant, neuroprotective, cardioprotective, hepatoprotective, anti-infective, and antiprotozoal properties [6,7].

Recently, several parasitic disorders, including malaria, leishmaniasis, and toxoplasmosis, can be treated using drugs delivered by nanoparticles [8]. Metal-organic framework nanoparticles, or MOFs, are crystalline materials made of metal ions or clusters that are regularly linked together by organic linkers. Extremely high internal and external surface areas and high permeability are features that differentiate them from others [9]. Thus, various loading techniques can be used to encapsulate medications within the pores or embed them on their outer surface. MOFs increase the solubility, bioavailability, and stability of pharmaceuticals. By extending the medication retention period and preventing the "burst effect," they can regulate the drug's release. Because of these special qualities, MOFs are receiving a lot of interest as drug delivery systems [10].

Recently, in the field of parasitology, experimental nanocomposites such as curcumin loaded on MOFs, bee venom loaded on MOFs, spiramycin loaded on MOFs, and ciprofloxacin loaded on MOFs were used in the treatment of experimental toxoplasmosis in infected animals [11].

To the authors' knowledge, the current study may be the first to evaluate the effect of SMC, SMC loaded on MOFs, P loaded on MOFs, and S loaded on MOFs in the treatment of chronic toxoplasmosis in experimentally infected mice. Hence, the current work was undertaken to evaluate the therapeutic effect of SMC used singly, in combination with the P-S regimen, and in conjugation with MOFs on experimental toxoplasmosis in immunosuppressed mice through parasitological evaluation of brain cyst count, immunological evaluation of serum IFN-γ levels, and examination of histopathological changes that occurred in mice brains following the administration of the drugs.

Material and Methods

Between February and April of 2023, our study was conducted at National Research Centre (NRC) in Giza, Egypt. The Veterinary Research Division, Department of Zoonotic Diseases, NRC, Giza, Egypt kindly contributed to the *T. gondii* avirulent strain (ME 49). Every eight weeks, Swiss albino mice were re-injected with 0.1–0.2 ml of brain homogenate from previously infected mice, which had roughly 100 cysts per millilitre. This procedure was used to maintain the strain [12].

Experimental animals

The present work was conducted using 54 male Swiss albino mice. The mice were selected from the NRC Animal House. Each mouse was between 20 and 25 g in weight and between 6 and 8 weeks in age. They were fed a typical meal consisting of 24% protein, 4% fat, 4-5% fibre, and water for the duration of the trial. The mice were maintained at 24 °C with 50–60% relative humidity [13, 14].

Following the protocol previously described, Dexazone 0.5 mg (Al Kahira Pharmaceuticals and Chemical Industries Company, Cairo, Egypt) was given orally to all mice at a dose of 0.25 μg/g/day starting 14 days before infection and continuing throughout the experiment to induce immunosuppression [15].

A 0.2 cc brain suspension containing twenty *T. gondii* cysts was given orally to all mice (except those in GI) to induce a persistent infection [16].

Animal groups

Mice were divided into 9 groups as described in Table 1.

Treatment preparations

Pyrimethamine, sulfadiazine, and SMC powders were obtained from Sigma-Aldrich, CO, 3050 Spruce Street, St. Louis, MO, USA. SMC25-MOFs, P-MOFs, and S-MOFs were prepared at the Chemical Industries Department, NRC.

The following approach was used to synthesize metal organic framework-based zirconium [UiO-66-$(COOH)_2$]: at room temperature, distilled water was used to disperse 1,2,4,5-benzenetetracarboxylic acid and zirconium tetrachloride (Sigma-Aldrich, CO, USA). For a whole day, the mixture was refluxed and stirred. After filtering the white precipitate that had formed, distilled water was used to wash it. Solids were mixed with distilled water, refluxed for sixteen hours, filtered, and then dried at thirty degrees Celsius to activate the process [16]. Measured amounts of MOFs were scattered into 50 ml of drug solutions at a particular concentration and swirled for two hours at 37 °C to evaluate the kinetics of drug loading. The nanoparticles were separated by centrifugation after the predetermined amounts of time, and a SHIMADZU spectrophotometer was used to measure the drug concentrations at 306 nm for sulfadiazine, 220 nm for SMC, and 225 nm for pyrimethamine. The amount of medicine loaded on the surface of MOFs was calculated from the following formula: $q_t = (\frac{(C0 - Ct)\,V}{W})$ where the drug concentration at the start of the loading process is C0 (mg/l), the drug concentration at the end is Ct (mg/l), the initial volume of drug solutions is V (L), and the weight of MOFs is W (g). Qt (mg/g) is the amount of drug loaded at any certain time [11, 16].

The cytotoxic effects of different concentrations of the newly synthesized nanocomposites (SMC-

MOFs, P-MOFs, and S-MOFs) were tested against normal human epithelial cell line: BJ (normal skin fibroblast using a multi-transaction translator (MTT) assay at the Bioassay-Cell Culture Laboratory, NRC. The 48-hour median lethal concentration values LC_{50} and LC_{90} were estimated [17].

Administration of the drugs

Fifty days post-infection, administration of the tested drugs was started and continued for ten consecutive days via oesophageal tube (once/day) following the doses mentioned above [12]. Then, all mice were sacrificed via cervical dislocation and decapitation, and blood samples were collected from them [18]. The effect of the drugs was estimated via parasitological, histopathological, and immunological parameters.

Parasitological evaluation (Brain cyst burden)

Following the sacrifice of the animals, a tissue homogenizer was used to homogenate one half of each brain in one millilitre of PBS (pH 7.4). Four drops of each homogenate, each containing 25 µl, were applied on glass slides. Then methyl alcohol and Giemsa stain were added to the slides. *T. gondii* brain tissue cysts were counted by using a light microscopy at a magnification of x 40. The following formula was used to detect the average number of cysts in each 1 ml brain homogenate of all mice: cysts count in 100 µl × 10 × 2 (2 halves of the brain). Reduction percentage of brain cysts in each group was determined as follows: Percentage of reduction = $(\frac{A-B}{A})x100$ (A = mean number of cysts in the infected untreated control group and B = mean number of cysts in each infected treated group) [19].

Histopathological assessment

The mice brains were preserved for 48 hours in 10% formalin. Following washing with distilled water and dehydration with ethyl alcohol, they were submerged in xylene and placed into paraffin blocks. To detect the pathological changes, slices were cut, stained with haematoxylin & eosin (H&E), and inspected using a light microscope (Zeiss, Germany) fitted with a high-resolution digital camera [19]. Glial cell counts and photomicrograph analysis were done using Image J software [20].

Immunological evaluation

Using a sandwich enzyme-linked immunosorbent assay (ELISA) kit from Wuhan Fine Biotech Co., Ltd., China, IFN-γ was detected in sera of all mice in the study groups. Using a microplate reader (Stat fax-2100, wavelength: 450 nm), at 450 nm the optical density (O.D.) absorbance was determined. We utilized the standard curve to detect IFN-γ concentration.

Statistical Analysis

The data is shown as mean plus standard deviation (SD). The data was analyzed using SPSS version 20 software. An ANOVA (F) was utilized, along with a post-hoc test, to compare factors among the different study groups. $p<0.05$ was used for significant results, $p<0.001$ for extremely significant results, and $p>0.05$ for non-significant results.

Results

Characterization of MOFs

SEM images of UiO-66–$(COOH)_2$ before and after loading the tested drugs showed the octahedral crystals. They suggest that highly crystallines UiO-66–$(COOH)_2$ were formed without impurities. After loading the drugs on UiO-66–$(COOH)_2$ SEM analysis revealed that the surface of MOFs seemed rougher than the surface before loading the drugs. The morphology and the size of the frameworks did not change after incorporation of the drugs supporting the stability of the frameworks (Figure 1).

Results of in vitro bioassay of the drugs loaded on MOFs

LC_{50} of P-MOFs and S-MOFs were 36.9 and 32.1 µg/ml, respectively. LC_{90} of P-MOFs and S-MOFs were 69.5 and 60.9 µg/ml, respectively. SMC-MOFs at 100 µg/ml increased the growth of the tested cells in 48 hours by 43.8%. It had no cytotoxic effect *in vitro* (Table 2).

Parasitological results (brain cysts burden)

Counting of *T. gondii* brain cysts in various study groups showed a highly statistically significant difference between all infected treated groups and the infected untreated group ($p<0.001$). The least mean number of brain cysts, 282.40 ± 15.33, with percentage of reduction 70.54%, was detected in GⅣ f by SMC25-MOFs, P-MOFs, and S-MOFs treatment, with a statistically significant difference when compared to other infected treated groups except GⅣe, whereas the highest mean number of brain cysts, 727±19.56, with reduction percentage 24.1%, was detected in GⅣb, with high statistically significant difference when compared to GΠ (Table 3).

Histopathological results (brain sections)

GI showed a normal histological structure of the cerebral cortex. The mean number of glial cells was 0.2 ± 0.4 (Fig. 2a, Table 4). **GΠ** showed profound histopathological changes in brain sections. These changes include distortion of neuronal architecture, presence of shrunken dead neurons with eosinophilic cytoplasm, inflammatory cells infiltration, congestion of the blood vessels with peri-vascular cuffing, and oedema. A noticeable proliferation of glial cells (diffuse gliosis) was detected. The mean number of glial cells was 103.4 ± 14.3 (Fig. 2b, Table 4). **GⅢ** revealed a noticeable regression of

brain tissue inflammation as a result of treatment with P-S regimen. The gliosis became focal. The mean number of glial cells was 32.8 ± 3.7, with a statistically significant difference when compared to GΠ (Fig. 2c, Table 4). **GⅣa** revealed a partial improvement in brain tissue inflammation with distortion of the neuronal architecture. The mean number of glial cells was 52.2 ± 10.5 (Fig. 2d, Table 4). **GⅣb** showed a partial regression of brain tissue degeneration, and presence of shrunken dead neurons with eosinophilic vacuolated cytoplasm. The mean number of glial cells was 61.2 ± 33.6 (Fig. 2e, Table 4). **GⅣc** demonstrated a considerable improvement in the pathological changes. The mice brains began to return to their original structure as a result of using a combination of SMC25, and P-S. The mean number of glial cells decreased to 6 ± 4.2 (Fig. 2f, Table 4). Regarding **GⅣd** there was a significant reduction of the histopathological changes. The mean number of glial cells was 17.8 ± 5.5 (Fig. 2g, Table 4). **GⅣe** showed a noticeable regression of the pathological changes. The mean number of glial cells was 37 ± 3.9 (Fig. 2h, Table 4). **GⅣf** showed minimal improvement in the pathological changes with abundant inflammatory cellular infiltrates. The mean number of glial cells was 78.6 ± 7.5 (Fig. 2i, Table 4).

Glial cells count

Photomicrograph analysis and counting of glial cells in the brain sections of all sacrificed mice by Image J software were done. The highest mean number of glial cells among the infected treated groups, 78.6 ± 7.5, was detected in group Ⅳf, with a statistically significant difference when compared to GΠ. However, the lowest mean number of glial cells among the infected treated groups, 6 ± 4.2, was detected in group Ⅳc, with a statistically significant difference when compared to GΠ. The mean numbers of glial cells in all infected treated groups had a statistically significant difference when compared to GΠ (Table 4).

Immunological results (IFN-γ level)

The mean levels of serum IFN-γ in all infected treated groups were significantly higher than those in GI and GΠ. GⅣf recorded the highest mean level of serum IFN-γ, 249.66 ± 18.12 pg/ml, with a statistically significant difference when compared to GI and GΠ. In GⅣf serum IFN-γ concentration increased by 182.23% (Table 5).

Discussion

T. gondii is a major cause of morbidity worldwide. Only a small number of medications, including the widely used P-S combination, have been available for clinical usage. To enhance treatment results, new drugs are required [21]. In the current work the therapeutic effect of SMC used singly, in combination with the P-S regimen, and in conjugation with MOFs on experimental toxoplasmosis in immunosuppressed mice were investigated. To the best of our knowledge, this research may be the first to assess the efficacy of SMC, SMC loaded on MOFs, P loaded on MOFs, and S loaded on MOFs in treating chronic toxoplasmosis in infected mice. SMC, P, and S were successfully incorporated into the pores of zirconium-based MOFs. The newly synthesized nanocomposites were tested with PXRD and SEM. All synthesized materials were crystalline and without any impurities, in agreement with a previously reported study by El-Shafey et al. [16].

In terms of the parasitological evaluation, the brain was chosen as a measure of infection severity because *T. gondi*i tissue cysts are primarily found in the central nervous system [22]. In the current study, all treatment regimens significantly reduced the mean number of brain cysts ($p<0.001$). Nevertheless, none of these regimens could eliminate the cysts completely from the mice brains. In agreement, El Naggar et al. [11] and Mohammad et al. [22] stated that the current *Toxoplasma* medications are unable to eradicate tissue cysts from the host completely.

In our work, the average number of brain cysts in the infected mice was reduced by both high and low dosages of SMC, notably with SMC50, demonstrating the effectiveness of SMC as an antiprotozoal treatment. Similarly, Elmahallawy et al. [6] stated that SMC at the same doses showed dose-dependent alleviation of *C. parvum* oocysts from *C. parvum*-infected mice. This may point to the efficacy of SMC as a potential antiprotozoal treatment. In agreement, several previous studies reported the therapeutic effect of garlic and garlic extracts against several parasitic diseases, including toxoplasmosis [23,24,25].

In the current work loading of SMC on MOFs achieved better therapeutic effect than using SMC alone in reducing brain cysts count, with high statistically significant difference when compared to the positive control group. Likewise, El-Shafey et al. [16] and El Naggar et al. [11] reported improved efficacy of drugs loaded on MOFs in the treatment of chronic murine toxoplasmosis.

The improved efficacy of the drugs loaded on MOFs may be due to the ability of nanoparticles to pass through physiological barriers. In addition, they improve the pharmacokinetics and therapeutic efficacy of the loaded drugs. Moreover, MOFs have been documented to have tremendous potential as antimicrobial materials, effectively combating a wide range of pathogenic microorganisms [11, 26].

Our results showed that SMC combined with P-S resulted in a 63.63% reduction in the mean number of brain cysts. This percentage was increased to 67.8% when SMC was combined with P-MOFs and

S-MOFs. The highest percentage of reduction in the average numbers of brain cysts, 70.54%, was achieved by combining SMC-MOFs with P-MOFs and S-MOFs. This increase in the percentage of reduction of brain cysts may be attributed to the synergistic effect of the combination therapy. Similarly, Bhatwalkar et al. [27] stated that combination therapy sometimes leads to a synergistic effect and better results than monotherapy. Moreover, nanoparticles can deliver drugs to specific tissues with controlled release of the drugs [28,29]. In accordance, several previous studies reported improved efficacy of drugs loaded on MOFs in the treatment of protozoal infections [11, 16, 30].

Regarding the histopathological assessment in the present study, the benchmark of evaluation was the examination of the brain sections from the non-infected untreated mice. These sections showed a normal histological structure of the cerebral cortex. The mean number of glial cells was normal. Microglia are brain-resident immune cells of the central nervous system that monitor and respond to damage-associated microenvironmental cues. They respond to neuropathology and promote inflammation during infections [31, 32].

Toxoplasma infection is known to induce microglial activation. Microglial cells produce IFN-γ, which is important in activating T cells. They trigger the host immune response to control the infection [33]. Glial cell overactivation can lead to neuroinflammation that results in various brain dysfunctions [34].

In our study, brain sections from infected untreated mice showed significant neuropathological changes, and the mean number of glial cells was markedly increased (103.4 ± 14.3). Similarly, Saleh et al. [35]; French et al. [22] and Nasr et al. [13] stated that *T. gondii*-induced neuroinflammation in the infected mice was associated with increased microglia activation and immune cell recruitment to the brain.

In the current study, all treatment regimens improved brain tissue inflammation, with a significant decrease in the mean number of glial cells. The best histopathological improvement was detected in GIVc. This improvement can be attributed to the synergistic effect of combination therapy [27].

Our results showed that SMC-MOFs demonstrated superior therapeutic efficacy as a single treatment, possibly due to the ability of nanoparticles to increase drug bioavailability, and drug concentration in the tissues [37,38].

Surprisingly, GIVe and GIVf showed lower efficacy than GIVc and GIVd in improving the inflammation in the brain tissues. These results were evidenced by a marked increase in the mean number of glial cells in GIVe and GIVf, an evident increase in the degree of inflammation. These results may be due to accumulation of MOFs in the tissues, as the multiple therapies loaded on MOFs, which may result in toxic effects [39,40].

We measured serum levels of IFN-γ to evaluate the immunomodulatory effect of the tested drugs. According to earlier researches, IFN-γ and cell-mediated immunity are essential for managing toxoplasmosis. Mice lacking IFN-γ are more vulnerable to *T. gondii* infection [21,41].

All mice were given dexamethasone to suppress their immune systems, following the procedure previously mentioned [15]. As a result, the mean serum IFN-γ levels in all research groups significantly decreased. When compared to the negative control group, there was a statistically significant difference in the mean level of serum IFN-γ between the positive and negative control groups. This outcome was in line with earlier findings in toxoplasmosis-infected mice used in other experiments [24]. The host immunological response to *T. gondii*, mostly through T cells, particularly T helper lymphocytes (Th1), was responsible for the increase in the mean level of serum IFN-γ after *T. gondii* infection. Pro-inflammatory cytokines like IFN-γ are produced in response to Th1 activation [12].

In our study, all treated groups recorded high significant increase in the mean levels of serum IFN-γ compared to the positive control group. The used regimen SMC25-MOFS, P-MOFS, and S-MOFS yielded the highest percentage of increase in the mean levels of serum IFN-γ, 182.23%. The increase in the mean level of serum IFN-γ in SMC-treated groups may be due to the immunomodulatory effect of garlic-derived compounds, which regulate inflammatory cytokines secretion [42]. Combination therapies achieved better results than monotherapy, possibly due to the synergistic action of the combination therapy [12].

In the current study, there was high significant increase in serum IFN-γ levels in infected mice treated with drugs loaded on MOFs. This increase may be due to triggering the immune response by zirconium with enhancement of the host immunity. Furthermore, nanoparticles enhance the therapeutic effect of the conjugated drugs, improving their efficacy [16]. In agreement, El-Zawawy et al. [43] and Elgendy et al. [38] reported a significant increase in serum IFN-γ levels in mice infected with *T. gondii* and treated with nanoparticles.

As explained in the current study, the immunological assessment results align with the parasitological assessments, indicating the effectiveness of combined therapies in treating experimental toxoplasmosis in immunocompromised mice.

Determining the therapeutic efficacy of studied medications is not as crucial as evaluating their potential toxicity. Therefore, to ascertain the possible toxicity of the studied medications, both in *vitro* and in *vivo* investigations are required. Without raising ethical issues, *in vitro* research allows for the exact investigation of the cytotoxic effects on particular mammalian cells. In contrast, investigations conducted *in vivo* demonstrate how medications are absorbed, distributed, and behave within the body [44,45]. In the present study, both *in vitro* and *in vivo* studies were done to evaluate the potential toxicity of the tested therapeutics.

First, MOF material design was completed and tested. Subsequently, an *in vitro* experiment was conducted to evaluate the cytotoxic potential of the produced nanocomposites [46].

LC_{50} of P-MOFs was 36.9 µg/ml. LC_{50} of S-MOFs was lower (32.1 µg/ml). Whereas no cytotoxic effect was encountered for SMC25-MOFs for 48 hours of exposure. SMC25 and SMC50 toxicity were not evaluated *in vitro* in this study. These doses were used safely *in vivo* in the current study, as no cytotoxic effects were encountered in the previously *in vivo* experimental studies [6,47].

One of the important results in this study is the documentation of combined SMC-MOFs, P-MOFs, and S-MOFs treatment cytotoxic effects on brain tissues on these mentioned combined doses. In contrast, a single loaded drug on MOF exhibited no cytotoxicity effect. Our results point out the fact that predicting the toxic effects of MOFs is a crucial and hardly predictable issue. In accordance, Ettlinger et al**.** [46] indicated that it is very difficult to estimate the harmful impact of the same MOF nanoparticle lines.

Based on both aspects of therapeutic efficacy and potential toxicity of the tested therapeutic drugs in this study, SMC (SMC25 and SMC50) showed anti-*Toxoplasma* activity unconjugated, conjugated with P-S, and MOF-loaded single, offering a safe therapeutic agent for toxoplasmosis. However, multiple loaded-MOFs combined therapy should be re-evaluated by various future *in vivo* studies as it exhibited high efficacy and cytotoxicity effects in the same context as therapeutic regimens for toxoplasmosis.

The chemical and physical properties of MOFs are remarkable. By addressing the possibility of toxicity and potential negative side effects, "safe-and-sustainable-by-design" solutions can be provided that find their way into real-world applications [46]. Thus, further evaluation of the therapeutic efficacy and potential toxicity in preclinical models is necessary to provide insightful feedback for the continued optimisation of MOFs therapy [48].

To the best of our knowledge, this study may be the first to assess the effect of SMC, SMC-MOFs, P-MOFs, and S-MOFs on the treatment of chronic toxoplasmosis infected-mice. The current study's findings should provide some initial direction and hints for future investigation.

Conclusion

The present study revealed that drugs loaded on MOFs have anti-*Toxoplasma* effect on chronic toxoplasmosis in immunosuppressed mice. Combined SMC with P-S therapy yielded the safest and best therapeutic response given the toxicity effects of MOFs found in histopathological examination of treated mice brains. However, monotherapy (SMC) coupled with MOFs could be a subsequent satisfactory alternative, till the detailed toxicity potential of MOFs is fully elucidated. SMC may be a safe and beneficial adjuvant treatment to the traditional treatment of toxoplasmosis. The absolute toxicity of multiple therapeutics and MOFs combinations needs to be verified by conducting wide-scale *in vitro* and *in vivo* cytotoxic assays on various microorganisms.

Nevertheless, this study confirms the promising activity of MOFs as drug delivery platforms. Thus, further investigations are needed to confirm their optimum doses as well as their exact mechanism of action against parasitic infections. Additional studies are needed to clarify the optimum therapeutic dosage of SMC in the treatment of toxoplasmosis, be it alone or coupled with nanoparticles, especially in immunocompromised groups and those at risk of congenital infection sequelae. Further studies are required to investigate the uses of SMC and MOFs in different forms and combinations in the treatment of other parasitic diseases in general.

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Conflict of Interest

“The authors declare that there is no conflict of Interest”

Author's contributions

“Authors contribute equally in this work”

Ethical approval

The protocol of this study was approved by the Ethical Committee of Kasr Al-Ainy School of Medicine and the Institutional Animal Care and Use Committee (IACUC) of Cairo University (approval

number: CU, Ⅲ-F-44-22). Animals were handled according to National Institutes of Health (NIH) guidelines for animals' experiments. All the experiments were carried out according to Clinical and Laboratory Standards Institute (CLSI) guidelines and the institutional animal care guidelines of NRC.

TABLE 1. Animal grouping

Group (6 mice each)	Group description	Drug	Dosage (mg/kg)
GI (Negative control)	Non-infected untreated	----------	---------
GΠ (Positive control)	Infected untreated mice	------------	---------
GⅢ (P-S treated group)	Infected treated with pyrimethamine (P) and sulfadiazine (S)	Pyrimethamine Sulfadiazine	12.5 mg/kg/day [12]. 200 mg/kg/day [12].
GⅣa (SMC50 treated group)	Infected treated with S-methylcysteine (High dose)	SMC50	50 mg/kg/day [6].
GⅣb (SMC25 treated group)	Infected treated with S-methylcysteine (Low dose)	SMC25	25 mg/kg/day [6].
GⅣc (SMC25, P-S treated group)	Infected treated with SMC25, P-S	SMC25 Pyrimethamine Sulfadiazine	25 mg/kg/day [6]. 12.5 mg/kg/day [12]. 200 mg/kg/day [12].
GⅣd (SMC25-MOFs treated group)	Infected treated with SMC25 loaded on MOFs	SMC25-MOFs *	
Group Ⅳe (SMC25, P-MOFs, and S MOFs treated group)	Infected treated with SMC25, P loaded on MOFs, and S loaded on MOFs	SMC P-MOFs ¥ S-MOFs #	25 mg/kg/day [6].
Group Ⅳf (SMC25-MOFs, P-MOFs, and S-MOFs treated group)	Infected treated with SMC25-MOFs, P-MOFs, and S-MOFs	SMC-MOFs P-MOFs S-MOFs	25 mg/kg/day

* SMC25-MOFs was used at the same dose of SMC25. ¥ P-MOFs was used at the same dose of pyrimethamine.
# S-MOFs was used at the same dose of sulfadiazine.

TABLE 2. LC_{50} (μg/ml) and LC_{90} (μg/ml) of the tested samples.

Sample	LC_{50} (μg/ml)	LC_{90} (μg/ml)	Percentage of mortality of the cells at drug concentration 100 μg/ml
P-MOFs	36.9	69.5	95%
S-MOFs	32.1	60.9	96%
SMC-MOFs	--------	--------	Growth of the tested cells increased by 43.8%
Negative control	--------	--------	0 %

TABLE 3. post-hoc multiple comparisons regarding brain cysts count of different study groups expressed as mean ± SD and reduction percentage (%).

Animal group	Brain cysts count Mean ± SD	Reduction %
GΠ	958.4 ± 63.31	----------
GⅢ	462.4 ± 51.44 [a]	51.75
GⅣa	495.4 ± 14.22 [a]	48.3
GⅣb	727±19.56 [abc]	24.1
GⅣc	348.6 ± 55.17 [abc]	63.63
GⅣd	433.8 ± 51.62 [a]	54.74
GⅣe	308± 17.89 [abc]	67.8
GⅣf	282.4 ± 15.33 [abc]	70.54

ANOVA test with post-hoc Tukey HSD test, [a] High statistically significant versus GΠ; $p<0.001$. [b] High statistically significant versus GⅢ; $p<0.001$. [c] High statistically significant versus GⅣa: $p<0.001$.

TABLE 4. Comparison between all study groups regarding number of glial cells expressed as mean ± SD.

Group	Mean numbers of glial cells ± SD
GI	0.2 ± 0.4
GII	103.4 ± 14.3
GIII	32.8 ± 3.7 [a]
GIVa	52.2 ± 10.5 [a]
GIVb	61.2 ± 33.6 [a]
GIVc	6 ± 4.2 [a]
GIVd	17.8 ± 5.5*
GIVe	37 ± 3.9 [a]
GIVf	78.6 ± 7.5 [a]

[a] Statistically significant compared to the infected-untreated group (GII). *p*-value<0.05.

TABLE 5. Comparison between all study groups regarding mean levels of serum IFN-γ (pg/ml) expressed as mean ± SD and increase percentage (%).

Group	Mean levels of serum IFN-γ (pg/ml) ± SD	Increase %
GI	32.76 ± 8.45	---------
GII	88. 46 ± 8.43 [a]	---------
GIII	146.9 ± 11.49 [ab]	66.06
GIVa	137.39 ± 7.26 [ab]	55.31
GIVb	113.3 ± 14.12 [a]	28.08
GIVc	195.02 ± 15.86 [ab]	120.46
GIVd	179.39 ± 13.43 [ab]	102.79
GIVe	219.58 ±20.23 [ab]	148.22
GIVf	249.66 ± 18.12 [ab]	182.23

[a] Statistically significant versus GI. *p*-value <0.001. [ab] Statistically significant versus GII. *p*-value < 0.001.

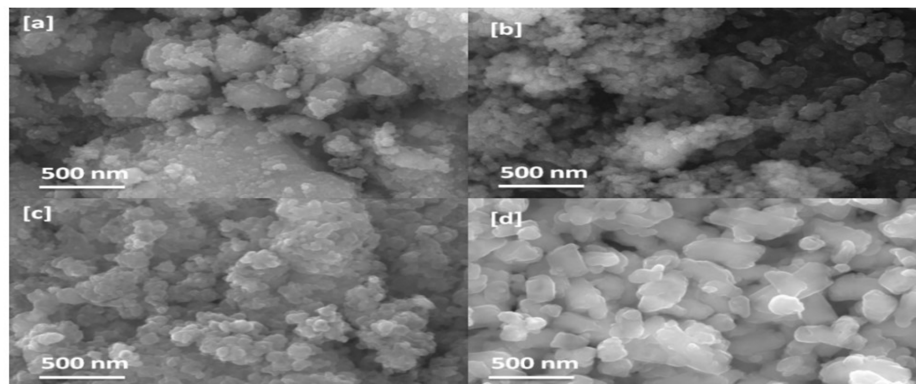

Fig. 1. SEM image of tested drugs loaded on MOFs (1a: UiO-66–$(COOH)_2$, 1b: S-MOFs, 1c: SMC-MOFs, and 1d: P-MOFs).

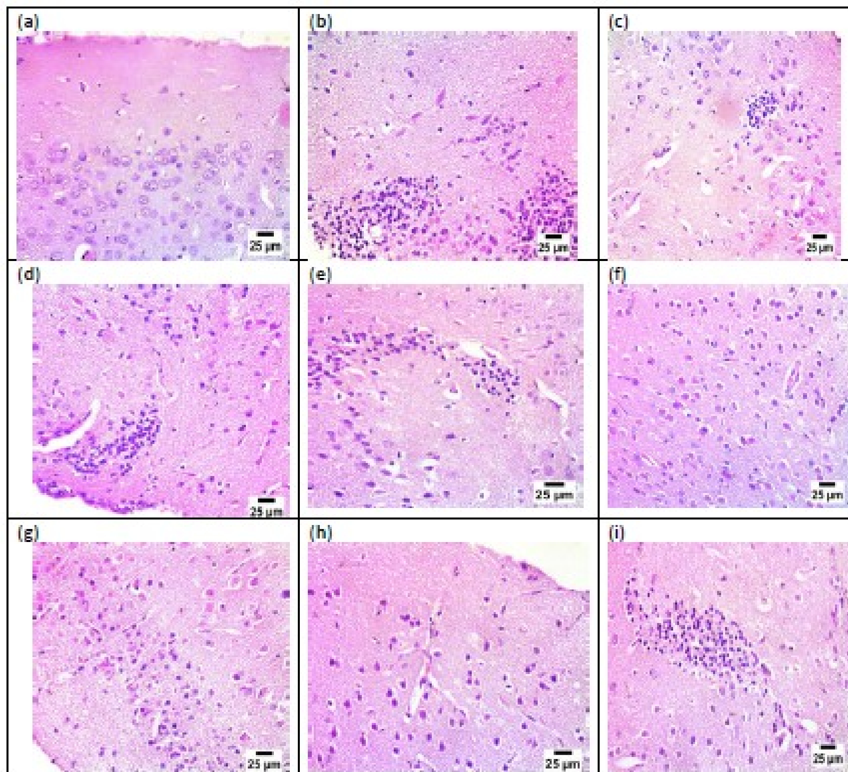

Fig. 2. Photomicrograph of brain sections of different study groups (Hematoxylin and Eosin, scale bar 25 µm, x400). a GI showing normal histological structure of the brain. b GII showing shrunken dead neurons with eosinophilic cytoplasm (red arrow), proliferation of glial cells (black arrow). c GⅢ showing shrunken neurons with pyknotic nuclei (blue arrow), focal gliosis (black arrow). d GⅣa showing focal gliosis (black arrow), shrunken neurons with eosinophilic cytoplasm (red arrow). e GⅣb showing focal gliosis in the cerebral cortex (black arrow). f GⅣc showing shrunken dead neurons with eosinophilic cytoplasm (red arrow), presence of nuclear pyknosis in some neurons (blue arrow), associated with minimal glial cells proliferation. g GⅣd showing nuclear pyknosis in some neurons (blue arrow), and shrunken neurons with eosinophilic cytoplasm (red arrow). h GⅣe showing shrunken neurons with nuclear pyknosis in cerebral cortex (blue arrow. i GⅣf showing focal gliosis (black arrow).

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تقييم التأثير المحتمل لاس ميثيل سيستين بمفرده ومتحدا مع الجسيمات النانوية من الأطر المعدنية العضوية علي العدوي التجريبية بداء التوكسوبلازما في فئران التجارب المثبطة مناعيا

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الملخص

أجريت هذة الدراسة لاستقصاء التأثير العلاجي لمادة الاس ميثيل سيستين منفردا ومتحدا مع البيريميثامين والسلفاديازين ومقترنا مع الجسيمات النانوية من الأطر المعدنية العضوية على داء التكسوبلازما المزمن في فئران التجارب المثبطة مناعيا. تم استخدام اربعة وخمسون فارا وتم تقسيمهم الي تسع مجموعات حسب النظام العلاجي المتبع. وتم عدوي للفئران عن طريق اعطاءهم حويصلات التوكسبلازما عبر الفم و بدأ علاج الفئران بعد خمسين يومًا من الإصابة لمدة عشرة أيام متتالية. شمل تقييم التأثير العلاجي لكل نموذج علاجي علي عد حويصلات التوكسوبلازما الموجودة بمخ الفئران وفحص أنسجتهم الدماغية وقياس نسبة الانترفيرون في الدم. سجلت المجموعة المعالجة بالاس ميثيل سيستين و البيريمثامين والسلفاديازين المحملين علي الجسيمات النانوية من الأطر المعدنية العضوية أعلى نسبة انخفاض في متوسط أعداد حويصلات التوكسوبلازما الموجودة بمخ الفئران و أعلى نسبة زيادة لمستويات الانترفيرون . ومع ذلك، حدثت زيادة واضحة في التهابات الأنسجة الدماغية في هذه المجموعة. نستنتج من الدراسة ان الأدوية المحملة على الجسيمات النانونية من الأطر المعدنية العضوية لها تأثير مضاد للتوكسوبلازما المزمنة في الفئران المثبطة مناعيا.

الكلمات الدالة: التكسوبلازما ، الانترفيرون، العدوي المزمنة ، الجسيمات النانوية.