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Possible candidates against the parasite *Toxoplasma gondii*: protocol of a systematic review

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Abstract

Introduction: Toxoplasma gondii is a parasite capable of infecting humans and other warm-blooded animals, that it is estimated to have chronically infected a third of the world population. While mostly asymptomatic in immunocompetent patients, it is considered a serious disease in immunocompromised patients, with potentially fatal consequences. The current treatment method used can trigger numerous negative side effects. The aim of this review is to evaluate current available pre-clinical studies regarding potential new candidates to be used against the parasite Toxoplasma gondii and its different life forms. Methods and Analysis: The authors will conduct a systematic review of all available pre-clinical studies. The search will cover the period between 2014–June 2019 and include studies that detail one or more of IC50, CC50 and SI values. The information and data on the new compounds will be collected from scientific databases - such as PubMed, Science Direct, Scopus, ISI Web of Science and Wiley Online Library -, and their potential as possibly future safer alternatives to the current medical treatment in use will be evaluated. Study selection will follow the PRISMA guidelines and study quality will be assessed by the GRADE methodology. Ethics Statements: While we accept that Ethics guidelines vary across different institutions and countries, approval from an Ethic Committee will be an important factor taken into consideration during study selection.

1. INTRODUCTION

1.1. Background

Toxoplasma gondii is an obligate intracellular parasite, capable of infecting humans and other warm-blooded animals. *Toxoplasma gondii* has a worldwide distribution, which makes its associated infection one of the most common in humans and warm-blooded animals. It has been documented in virtually every species of mammal and even on several species of birds (Dubey, 2010).

This infection, adequately named Toxoplasmosis, can be acquired through different routes. The most common routes are through ingestion of oocysts from the environment and contact with cat faeces, ingestion of tissue cysts in undercooked meat and under-washed raw vegetables and fruits, and by transplacental transmission of tachyzoites (Dubey, 2008).

It is estimated that, approximately, a third of the population worldwide is chronically infected with *Toxoplasma gondii* (Ben-Harari et al., 2017).

While mostly asymptomatic in immunocompetent patients, Toxoplasmosis is considered a serious disease in immunocompromised patients, such as HIV/AIDS patients, cancer patients, and organ transplant recipients. Because *Toxoplasma gondii* may remain within the host through its life span - usually in a latent, subclinical infection -, there is a possibility of a spontaneous reactivation, which is more likely to occur in immunocompromised patients, and can be fatal. Screening for *Toxoplasma gondii* is generally only done in pregnant women, however it's not

mandatory in every country as some have no prenatal program of surveillance (ECDC, 2018; EFSA & ECDC, 2018).

Treatment for an infection by *Toxoplasma gondii* usually falls on the use of Pyrimethamine, an antimalarial drug, sometimes combined with an antibiotic drug (like Sulfadiazine or Clindamycin) (Montoya & Liesenfeld, 2004). Besides having the ability to trigger a myriad of side effects, the use of Pyrimethamine has a high rate of inducing toxic side effects that may affect several areas of the body. It can affect the gastrointestinal, nervous, respiratory and cardiovascular systems, can cause several hypersensitivity, hematologic and metabolic problems, and in very rare cases may also lead to oncologic problems (Alday & Doggett, 2017; CDC, 2018; McPhillie et al., 2016; HSS, 2019).

One quality that makes *Toxoplasma gondii* harder to deal with is its ability to cross the blood–brain barrier and establish a persistent infection in its bradyzoite stage, that has a high drug-resistance (Alday & Doggett, 2017; McPhillie et al., 2016). While the parasite is capable of switching between its tachyzoite stage – which is much easier to eliminate – and its bradyzoite stage spontaneously (usually when the parasite comes across an suitable host cell environment), stress triggered by the drugs used in the treatment against it may also induce differentiation (Lueder & Rahman, 2017; Skariah, McIntyre, & Mordue, 2010).

There have also been increasing reports of Pyrimethamine drug resistance (Doliwa et al., 2013; Meneceur et al., 2008; Sims, 2009). This combined with the multitude of side effects caused by the primary method used to treat toxoplasmosis and with the inability of current treatments to eliminate all stages of this parasite, create the necessity of finding new ways to treat infections caused by this parasite that has a wide worldwide distribution.

1.2. Objective

The objective of this systematic review protocol is to detail the methodology that will be used in a systematic review to assess what new compounds that are being studied in laboratory as new possible candidates with potential to be used against the parasite *Toxoplasma gondii*, focusing only on studies still in initial pre-clinical stages, not on clinical trials.

2. METHODOLOGY

The current study is in accordance with the PRISMA-P statement for systematic review and meta-analysis protocols (Moher et al., 2015; Shamseer et al., 2015).

2.1. Eligibility criteria

For the identification of studies regarding possible new compound candidates with anti-T.gondii effect, online databases will be browsed from January 2014 until June 2019, for articles and articles in press written in English.

2.2. Information sources

The following databases will be browsed within the aforementioned period: PubMed, Science Direct, Scopus, ISI Web of Science and Wiley Online Library

2.3. Search strategy

For this purpose, a search using a combination of the following keywords: "*Toxoplasma gondii*", "Treatment", "Drugs", "Tachyzoites" and "Bradyzoites" will be conducted. In order to avoid missing any articles, after database searching, the reference list of the relevant papers found will also be screened manually. The initial exclusion criteria is the absence of the name of the parasite in the article's title.

2.4. Study records

2.4.1 *Data Management and Data Selection*

The articles retrieved from this research will be imported to EndNote. After initial title screening and the removal of duplicated papers, abstracts will be reviewed and eligible articles selected for full-text analysis.

2.4.2 *Collection Process*

As each combination of keywords is entered, two exclusion phases will be applied:

1. Through search filters, the following criteria will be considered:
   - i Date: Articles published as of 2014 until June 2019;
   - ii Type of document: articles and articles in press;
   - iii Type of source: journal;
   - iv Language: English;
2. Articles will be deleted if any of the following conditions are met:
   - i Absence of the name of the parasite in the article's title;
   - ii The studies fail to mention approval (or lack of need of approval) of an ethic committee.

2.5. Data items

Data from relevant studies will be compiled into a Microsoft Excel datasheet:

1. General information: first author, year of publication and country;
2. Characteristics of the in vitro study: Cell line, compound(s) name(s), T.gondii strain type, IC50 values (minimum inhibition concentration), CC50 values (cytotoxic concentration), and SI values (Selectivity index), and the compound method of action;
3. If a study also has an in vivo part, a separate datasheet will be created similar to point 2;
4. Ethics statement,
5. Main limitations of the study;
6. Quality assessment.

Tables will be assembled with the compiled information described in the aforementioned section.

2.6. Outcomes and prioritization

The main goal will be to find which compounds that are currently being studied and assess if they have prospective anti-T.gondii effect, and are potentially safer that the current medical treatment in use through evaluation and comparison of values of IC50, CC50 and SI.

2.7. Risk of bias in individual studies

Risk of bias will be evaluated for each individual study analysed making use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate quality of evidence. Data acquired will be analysed according to the intended objectives of this review; goals and objectives, evaluated variables, applied methods and equipment, evaluation procedure, and compliance with ethical standards will be under analysis.

2.8. Data synthesis

Given the variety of results expected, performing a meta-analysis will likely not be possible. Therefore, the synthesis of data will be done through a narrative, with textual descriptions of each article, exploring relationships within and between studies based on the above-mentioned data tables assembled. Bias through the GRADE method will also be taken into account when analysing data and attempting to establish comparisons of results found.

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