



SDI Review Form 1.6

Journal Name:	International Journal of TROPICAL DISEASE & Health
Manuscript Number:	2014_IJTDH_13391
Title of the Manuscript:	Therapeutic arsenal against leishmaniases: a review
Type of the Article	Review Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<http://www.sciencedomain.org/page.php?id=sdi-general-editorial-policy#Peer-Review-Guideline>)



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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	1- The title does not seem appropriate, as it suggests that the authors will discuss the treatment options available to treat the disease, but a great part of the manuscript refers to alternatives still in the early stages of research (<i>in vitro</i> and <i>in vivo</i> assays), as the natural products and other derivative of plants. 2- The first, second and third paragraphs (Page 1, lines 23-43), which deal with the disease, are very confuse, with an excess of details. I suggest presenting only relevant information and, thus, make the text more clear and straight. 3- The Figure 1 shows an outdated proposal for the chemical structures of the pentavalent antimonials, when it is currently known that these structures are not correct. I suggest a further reading on the reference 14 and Berman JD, (Chemotherapy for Leishmaniasis: Biochemical Mechanisms, Clinical Efficacy, and Future Strategies. Rev. Infect. Dis. 1988; 10 (3): 560-586) to gather information to update the figure with more appropriate structures. 4- On the mechanism of activity of pentavalent antimonials (Page 3, line 106), the authors state that "there are indications that trivalent antimony is substantially more potent than its pentavalent oxidation state...". This sentence contains incorrect information, as it is currently	1. We ask for reconsideration on this point. We understand that the title is appropriate since it relates to the therapeutic arsenal in general. It was not mentioned that the manuscript would deal only those medicines available in the market. The goal is also clear in the abstract. 2. We agree. These three paragraphs were summarized in two (first and second ones). 3. We agree and corrected it. 4. We ask for reconsideration on this point. According Frézard et al., 2001 (one of your cited references), the mechanism proposed by Ephros et al. (1999) was refuted. The proposed mechanism of action in this manuscript is therefore the most current, besides this our text refers to it as hypotheses. Regarding the update of the molecular and biochemical effects of antimony, we agreed and added (Frézard et al., 2009). 5. We agree, this information was included. 6. We agree. The sentence is non-sense because the word "not" is missing. We corrected to: "When multiple consecutive doses are not

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	known that not only pentavalent antimony is more potent against the parasite but it also more toxic to the host. Therefore, it is not used in therapy (See Ephros et al., 1999 and Carió et al., 2000). In addition, there is new information about molecular and biochemical effects of antimony available in the literature that should be added to the manuscript (e.g., Baiocco et al.; Frézard et al, 2001; Denton, et al, 2004; Frézard, 2009). 5- On page 8, line 309, referring to miltefosine, the authors state that "...despite not knowing exactly how it acts as leishmanicidal in the human body, interacts with the protozoan's cell membrane, causing its death. This is attributed to the close similarity between protozoan and human plasma membranes". If this similarity was so high, it would be expected that miltefosine would be toxic for the mammalian cells as it is to the parasites, thus making its therapeutic use very dangerous, what is not the case. Therefore, this sentence should be revised. 6- On page 3, line 148, the authors state that "When multiple consecutive doses are administered, the dosage is not fulfilled, resulting in drug resistance"... Actually, due to rapid renal elimination of pentavalent antimonials, multiple injections are required when using high doses (20mgSb⁵⁺/kg/day). The resistance to treatment may occur by interruption of daily injections or by the use of lower dosages that may allow for some species to develop resistance. 7- On page 4, line 187 the authors describe the dosage regimen for liposomal amphotericin B, however	<u>administered, the dosage is not fulfilled, resulting in drug resistance [33].</u> <u>7. We agree. This information was included.</u> <u>8. We agree and corrected/rewrote it.</u> <u>9. We agree and corrected it.</u> <u>10. One reference of Muzitano et al. 2006 and the reference of Vila-Nova et al. 2012 (on rutin) are already contained in the manuscript (original citation numbers: 84 and 82, respectively). As the manuscript is quite extensive, we chose to highlight quercetin, due to its relevance among the flavonoids for this application. We agree about the Muzitano et al. 2006 and 2009 references and included them.</u> <u>11. We agree and corrected it.</u> <u>*All the changes from your comments are highlighted in green.</u>
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	similar information about treatment with the free form of amphotericin B (deoxycholate), which is still the most used as it is cheaper, is not shown. To inform such data would be very relevant in for the context of this reviewpaper. 8- On page 5, line 215 the authorstry to explain the hepatotoxicity of amphotericin B, however, is well established that the most common problem associated tothis drug is the development of nephrotoxicity. Thus, such fact should be addressed in the text. 9- The text section about paromomycinwas placed before pentamidine, butthe latter has been used longer in the treatment of leishmaniasis. It would be interesting to maintain a history-related order to better lecture the reader on the evolution of leishmaniasis treatment. 10- Currently, in the literature, there is plenty of relevant information about flavonoids derived from plant extracts (page 11, lines 388-415) and these datawere not included in the manuscript(e.g., Muzitano et al., 2006 and 2009). In addition, the manuscript lacks significantdataabout the leishmanicidal properties rutin extracted from <i>Dimorphandra Gardneriana</i> grains. 11- Liposomes formulations have been developed to minimize the commented nephrotoxicity caused by amphotericin B (Page 15, line 505). See your reference 34.	
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<u>Minor</u> REVISION comments	Review manuscripts must have a focus. Some bring more clinical information (clinical trials, case series, case reports, or details about the treatment as dose regimen, indications/ contraindications, adverse effects, etc), while others prefer to give general details like mechanism of action and biochemical / pharmacological effects. My suggestion is to concentrate your effort in one of these branches and just illustrate it with a few more details. I think it will make the reading more enjoyable	In order to meet the requests of all reviewers (some of them considering the current information as important), the topics have been kept and the immunotherapeutic approach (request of another reviewer) was included (highlighted in grey).
<u>Optional/General</u> comments	I suggest a detailed revision of the English by someone native in the language. Also, some sentences were written joined together, thus a comprehensive review of the manuscript is required.	The manuscript was also completely revised by a native, as suggested. For some reason, the file was unformatted, to which we apologize. We give attention to this in the new document formatting. These changes are highlighted in yellow.

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