Author’s response to reviews

Title: Interactions of clinical relevance associated to concurrent administration of prescription drug and food or medicinal plants: a systematic review protocol

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Author’s response to reviews:

REVIEWER #1

Introduction

Line 79-80

"Consequently, they are often avoided in medical prescriptions or quickly treated when clinically recognized". - it would be nice to have a reference or two for this.

ANSWER: We added a reference on line 80 (citation 1).

Line 92-94

"Likewise, concurrent administration of dairy products or those fortified with calcium and fluoroquinolones (ciprofloxacin) decreases drug bioavailability and could cause drug resistance to this class of antibiotics" - I would suggest substituting reversing the order of the sentence for clarity i.e. "Likewise, concurrent administration of fluoroquinolones (ciprofloxacin) and dairy products or other foods fortified with calcium can decrease the drug's bioavailability and could result in resistance to this class of antibiotics"

ANSWER: Lines 92 and 94 have been updated with the text suggested by the reviewer (current lines 92 to 95).

Line 102-105

"Moreover, in 2010 published the "Guide for Drug Interactions Research" which contains a chapter especially committed to medicinal plants, herbal products, and food, thus highlighting the actual need to investigate their potential interactions with prescription drugs" - it looks like you dropped a word maybe? Its also a little unclear where its from... I think you're referring to
I would suggest "The 2012 "Guideline on the investigation of drug interactions" published by the European Medicines Agency contains chapters committed to food (Chapter 5) and herbal products (Chapter 6), thus highlighting the actual need to investigate their potential interactions with prescription drugs."

ANSWER: Lines 102 and 105 have been updated with the text suggested by the reviewer (current lines 103 to 106).

Line 105-109

"Correspondingly, the Regulatory Agencies of the European Union, the United States of America and Canada have established the obligation to mention on the label of herbal products, their possible interactions with prescription drugs, in case of confirmed evidence" - it would be nice to reference each of these documents/reports/legislation directly if possible.

ANSWER: Line 110 includes citations from the Regulatory Agencies of US (citation 22), European Union (citation 23) and Canada (citation 24).

Line 120-122

"Majority of drug-drug interactions are known and preventable, nevertheless little is known about pharmacological interactions between drugs and food or medicinal plants." - I think you dropped the "The". I would suggest "The majority of drug-drug interactions are known and preventable, nevertheless little is known about pharmacological interactions between drugs and food or medicinal plants."

ANSWER: Current line 121 has been updated with the correction suggested by the reviewer.

Line 135-140

"Thus, a systematic review in this topic would indirectly support the obtaining of a satisfactory result with prescribed pharmacological therapy and encourage among patients, nutritionists, pharmacists and doctors, the development of a culture of rational and responsible use of medicines with a focus on the appropriate combination with nutrients and medicinal plants." - this sentence seems clumsy. Maybe break it up into two?

ANSWER: The original sentence is divided into two, according to the suggestion of the reviewer (current lines 136 -141).
Methods

Overall, lovely methods - very comprehensive. I would include studies outside English and Spanish. Maybe suggest translating the studies and/or contact the author if you are unable to get a translation.

ANSWER: As an initial phase, this study includes studies in English (because most scientific publications are available in this language) and in Spanish (because it is the official language of Ecuador, the country where this systematic review is going to be developed).

The translation of studies published in other languages as well as the suggestion to contact the authors for the corresponding translation are valid and very welcome. However, at present, it is proposed to compile information in English and Spanish as an initial starting point. Then, studies published in other languages can be added and the period of the included studies also could be extended.

Discussion

No problems

Additional file 2.

Is this just an example for epilepsy? If so, you should make this clear in the text - or else expand the document out to include other illnesses/medications.

ANSWER: It was clarified that the search strategy in Pubmed for phenytoin and epilepsy is included as an example in Additional File 2 (current lines 210 and 211).

REVIEWER #2

Some thoughts:

There is already quite a lot known about ARs across certain pharmaceutical agents, certain foods, and certain herbs. Medically-trained personnel should have some knowledge of most of these interactions, therefore I disagree with the statement that information on drug-food/herb interactions is not widespread.

However, maybe what is lacking, is a better dissemination of this information across "all healthcare settings"? This could include different country settings, different levels of prescriber training, different levels of prescribing (i.e. drug therapy initiated by a prescriber or lay person), and how the food or herb is being used, e.g. as traditional medicine or simply as foodstuffs, etc.
This presents a large playing field, and my concern is that the proposed review, based on the presented protocol, will not properly capture all these differences.

ANSWER: If we compare the knowledge of drug-drug interactions vs. drug-food or drug-herb interactions, the latter has not been sufficiently disseminated across all healthcare settings. An additional problem is that in the consultation the medical doctor can determine which drugs cannot be administered together while, due to the great variety of foods and plants, it is more difficult to know them all. Therefore, it is not possible to alert to the patient about this type of interactions. Thus, this review aims to provide a reliable compilation of information on this type of interactions in such a way that medical doctors, pharmacologists, nutritionists, etc. can refer them to their patients in a timely manner, contributing to the prevention of this type of interactions.

Specific comments:

Major revisions:

The background of the current manuscript, and justification to this systematic review makes too many claims. The resulting systematic review - as with all reviews - can do no more than inform relevant stakeholders. I would advise to tone down the language.

ANSWER: Completely agree. The text was updated according to the reviewer's suggestion (current lines 136 -141).

Suggestions:

The protocol could benefit from being more specific: - Prescription drugs "of interest" - maybe be specific and explain the choice. As written, the list could include the entire pharmacopoeia.

ANSWER: It has been sought that the protocol could be useful to identify interactions of this type with any drug of the pharmacopoeia and the specific disease treated with that drug. For example, chronic diseases such as epilepsy, hypertension and diabetes have been cited as examples, which constitute those with which we will initiate this review. Of course, the protocol also aims to be useful for medication used in acute treatments (e.g. antibiotics).

Will vulnerable population groups e.g. pregnant or lactating women be included?

ANSWER: They are included in the group of adults since the exclusion criteria for pregnant or lactating women have not been indicated in the data extraction criteria.

Will heterogeneity between studies be assessed somehow, even though the summary will be narrative?
ANSWER: Heterogeneity will be evaluated through JBI and GRADE scale criteria (current lines 277 - 280). The GRADE scale is proposed in addition to the JBI criterion originally stated. The reference to GRADE scale is included.

Study limitations - will these be assessed using JBI checklists?

ANSWER: Yes, they will be evaluated using the JBI checklists and GRADE scale. The reference to GRADE is included (current lines 277-280).

Limitations of selected studies will be deeply discussed (line 297-8) - why only selected studies and not all studies? If just selected studies, how will these studies be selected?

ANSWER: With the term "selected studies" we refer to all those studies that fully meet the eligibility criteria of this systematic review. The eligibility criteria and type of included studies are indicated in detail on current lines 173-198. The process of selecting the studies is described in detail on current lines 217 to 231.

Unless otherwise clear in the literature, how will you distinguish between the specific disease name when the drug has more than one indication?

ANSWER: In the search strategy, the specific name of the disease is detailed so that according to the protocol, if the drug has more than one medical indication, the study is excluded if it does not focus on the therapeutic use of that drug for the treatment of the disease specified in the search strategy.

How will the narrative review be structured? Can you define this in advance?

ANSWER: The structure of the narrative review is described in current lines 284 through 301.

Lines 307-309: "...to date, there is no review on clinical characteristics and safety issues related to concurrent drug administration with food or plants..."

Some reviews (e.g. Deng et al (reference 24), and Ased et al., doi: 10.4140/TCP.n.2018.649) have been published, though are perhaps not exactly what the authors are proposing. The authors may wish to be clearer in describing how their systematic review will be different though complementary to the existing literature.

ANSWER: This systematic review does not analyze the drug-herb or drug-herb interactions separately for a particular drug used for the treatment of a specific disease but rather compiles both types of interactions in a single document making it more complete and easier to
disseminate among members of the health team and patients. For a better understanding of this idea, the text has been modified (current lines 309 to 323).

Finally, the PROPSERO registration states a 5-year turnaround for this review. Do you intend to re-run the searches before final manuscript submission?

ANSWER: We did not seek to re-run the searches but to develop at least five systematic reviews of drugs used to treat epilepsy, five for diabetes and five for hypertension by using this protocol during this period (5 years).