Author’s response to reviews

Title: Association between anthraquinone laxatives and colorectal cancer: protocol for a systematic review and meta-analysis

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Author’s response to reviews:

Reviewer #1:

Abstract

Page 2 Line: 13 reads "As no firm evidence exists to the potential association between the CRD42019125414 of…” please fix error

We agree with Reviewer 1 and we corrected the above-mentioned error as follows [page 4, lines 101-103]: “Since there is no clear evidence of the potential association between the use of oral AQ laxatives and the risk of CRC, we aimed to quantify this risk by performing a systematic review and meta-analysis.”

Background
The proposed mechanism by which AQs may exert a laxative effect and cause damage to epithelial cells is not convincing enough. What specific compound in AQs are responsible for this mechanism? And via what cellular path ways do they affect this? Sodium or potassium channels or cyclic AMP? Etc. The evidence from this review will be of interest to both experts in the field of oncology and lay people alike. Hence the need to have these groups of consumers in mind.

We agree with Reviewer 1 and we improved the Background (Introduction) section as follows: “In particular, two different mechanisms of action have been proposed: (1) an effect on large intestine motility resulting in accelerated colonic transit, thus reducing fluid absorption; and (2) an effect on secretion processes resulting in enhanced fluid absorption. At cellular level, one main target is the inhibition of the Cl−-channels across colon cells, contributing to the laxative effect [Emodin - A Secondary Metabolite with Multiple Ecological Functions in Higher Plants: https://www.jstor.org/stable/1513810?seq=1#metadata_info_tab_contents]. Moreover, Na+/K+-ATPase pump is inhibited by those 1,8-dihydroxyanthrones/anthraquinones bearing an additional phenolic hydroxyl group [Herbal Laxatives - Influence of Anthrones-Anthraquinones on Energy Metabolism and Ion Transport in a Model System: https://pubs.acs.org/doi/pdf/10.1021/bk-1998-0691.ch009].”

Methods

Any reason why authors choose to exclude clinical trials and randomized controlled trials? These are the highest form of evidence if you are looking for safety (although real world evidence from observational studies in the long term is important). You can only settle on observational studies if no clinical trials are found or evidence from trials found no adverse events (understandable due to their often-short duration of follow up and lack of latency). But to ignore these designs from the get-go is not advisable. Any evidence adduced in the end, in the absence of contribution from clinical trials, will be weak. Under data items, authors intend to collect information on randomization and blinding yet this type of study design are excluded in their study selection criteria outline about.

We agree with Reviewer 1 and, although we believe that due to their often-short duration of follow up and lack of latency RCTs are not the best methodology to find these kind of long-term adverse events (eg., colorectal cancer), now we also include RCTs, modifying the search strategy and correcting the entire protocol. We modified all the Protocol accordingly.

Any reason why the Newcastle-Ottawa Quality Assessment Scale is used instead of the Cochrane ROB tool for non RCT?

We usually applied this kind of tool. Based on our experience, the Newcastle-Ottawa Quality Assessment Scale is one of the most used tools. In our opinion, there are no substantial differences between the two scales.
Unit of analysis is unclear. Each intervention deals with participants. Therefore, your unit of analysis is participants as opposed to a body part of participants such as (eyes or teeth of participants) assuming these were the units the interventions were applied.

We consider the “trial arm” as the group of patients enrolled in the RCT and exposed to a specific treatment (in our case AQ laxatives), rather than a body part of participants.

Authors should consider including RCTs. There appears to be no restriction to the timing of outcomes. This need to be set a priori judging from prior studies, the reasonable time points within which adverse events could have occurred. For instances, if a participant takes AQ and after two weeks, receives a diagnosis of CRC would you attribute this to the consumption of AQs?

As reported above, we will also include RCTs, modifying the search strategy and correcting the entire Protocol. Furthermore, we will include any diagnosis of CRC in patient exposed to AQ laxatives for a period exceeding two weeks, taking into account the clinical characteristics of each patient and evaluating the events of CRC on a case-by-case basis. For this purpose, we will request data at the single patient level from authors of the included original studies. Thus, we improved the Timing section as follows: “Regardless of the time of onset, we will include any diagnosis of CRC in patients exposed to AQ laxatives for a period exceeding two weeks (“long-term” use). Then we will perform a stratification based on the latency time, taking into account the clinical characteristics of each patient and evaluating the events of CRC on a case-by-case basis. For this purpose, if necessary, we will request data at the single patient level from authors of the included original studies.”

Reviewer #2:

Title: Association between anthraquinone laxatives and colorectal cancer: protocol for a systematic review and meta-analysis

This protocol of planned systematic review tries to synthesize the safety of AQ products usage. It plans to fill evidences gap on long-term treatment with oral AQ laxatives and particularly focusing on the risk of colorectal cancer (CRC). It will provide valuable evidence on clinical decision making.

However the manuscript requires extensive language edition before publication.

We edited the manuscript, as suggested. All improvements and corrections are highlighted in red.

The following concerns should also be addressed

* "Short-term use (&lt;2 weeks) of AQa is generally safe" is written in manuscript many times without valid evidence/reference
We agree with Reviewer 2 and we corrected the Introduction section, adding new references as follows:

“The World Health Organization (WHO) has published monographs on safety, efficacy and quality control of Aloe, Cassia, Frangula and Cascara for their use as medicinal plants [World Health Organization, 1999. WHO Monographs On Selected Medicinal Plants, Vol. 1. World Health Organization, Geneva]. In the monographs, it is recommended that products containing AQ glycosides should not be used for longer than 1-2 weeks, due to the possible incidence of serious AEs, such as electrolyte imbalance.


In Germany, the Federal Institute for Medicines and Medical Devices has recommended not to use AQ laxatives for prolonged periods [Chan, K., & Lin, T. X. (2009). Treatments used in complementary and alternative medicine. Side Effects of Drugs Annual, 745–756. doi:10.1016/s0378-6080(09)03148-1].”

* Cite some of potential for inclusion while providing the rationale of the study to reason there ample studies for synthesis

We already described the rationale of the study in the Introduction section. To date, epidemiological data suggested an increased risk for CRC associated with the general use of laxatives, several of which contain AQ derivatives. For example, as reported by EFSA [Safety of hydroxyanthracene derivatives for use in food. Available at: https://www.efsa.europa.eu/it/efsajournal/pub/5090], five cohort studies were reviewed and an increased risk for CRC was found in all, however, only in two studies the results were statistically significant. Based on the studies reviewed by the European Medicines Agency (EMA) and the results of more recent large epidemiological studies, EFSA agreed with previous evaluations that the prolonged use of laxatives is a possible risk factor for CRC. Nevertheless, EFSA was of the view that better designed epidemiological studies (e.g., cohort studies with large sample size and proper control for confounding factors) investigating on the relationship between AQ laxatives use and CRC are needed. Thus, the importance to perform a systematic review and meta-analysis like the one we proposed.

* The choice of random-effects model or fixed effect model should be determined after assessing the heterogeneity

We agree with Reviewer 2 and we corrected the Measures of treatment effect section as follows: “All considered outcomes are based on dichotomous data. According to the assessment of statistical heterogeneity, if appropriate, for all considered outcomes, we will perform a meta-analysis using a random-effects model within a frequentist framework.”
* Some of the assertions are not cited; for example the statement 'Long-term use of AQs was associated with an increased risk of colorectal cancer (CRC)' is not cited.

In the Introduction section we already mentioned [Safety of hydroxyanthracene derivatives for use in food. Available at: https://www.efsa.europa.eu/it/efsajournal/pub/5090] the citation linked to EFSA document reporting the potential association between “long-term” use of AQs and CRC. Please, see lines 93-100.

Discussion is not totally cited.

We agree with Reviewer 2 and we added to our Protocol a Discussion section as follows:

“DISCUSSION

To the best of our knowledge, this systematic review and meta-analysis will provide the a comprehensive narrative synthesis and quantitative estimate of the risk of CRC in subjects exposed to a long-term treatment with AQ laxatives.

The pooled estimate will guide clinicians and policymakers in informing patients and governments about the risk associated to the use of products containing AQ laxatives. This risk could be greater for self-administered products that are easily available without a medical prescription.

Moreover, it will provide an estimate of the future global CRC burden in the context of the complementary and alternative medicine. Importantly, this systematic review will enable the identification of clinical, epidemiological, and public health gaps, thus outlining directions for further investigation.

The findings from the review will be disseminated in a peer-reviewed journal, and we will recommend or carry out research to bridge the identified gaps.

Strengths and limitations

A major strength of our study is the comprehensive review within six major databases in order to include all potential articles. Limitations include the heterogeneity in the sample size of the retrieved studies and quality of the study design. Furthermore, prospective studies with a sufficient follow-up period to observe the occurrence of CRC may be lacking.”

I have tried to edit the abstract part as follows, authors can adapt

Abstract:
Background: Anthraquinones (AQs) containing products are mainly used as laxative and have several biological effects and adverse events (AEs) related to their use. Long-term use of AQs was associated with an increased risk of colorectal cancer (CRC). We will systematically synthesize the evidence on potential association between AQs use and the risk of CRC.

Methods: We will search MEDLINE, Embase, Scopus, the Cochrane Library, Google Scholar, and Clinicaltrials.gov. We will also search the bibliographies of retrieved articles. Interventions will include products containing oral AQ laxatives, in particular AQs derived from rhubarb, senna, cascara, buckhorn, and aloe. Two review authors will independently screen title, abstract and full texts, and independently extract data from included studies. Primary outcome is number of subjects diagnosed with "CRC while secondary outcome will be number of melanosis coli cases. We will also consider all other AEs reported in the included studies, in particular: intestinal bleeding, alterations of gastrointestinal motility, and potential for dependence. Where possible and appropriate, for each outcome a meta-analysis will be performed.

Discussion: This protocol is prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines. The protocol gives an insight into the scope and parameters for the systematic review to be carried out.

Systematic review registration: The protocol was registered in international prospective register of systematic reviews (PROSPERO), ID = CRD42019125414

We thank Reviewer 2, adapting the Abstract section as follows: “Introduction: Products containing anthraquinones (AQ) are mainly used as laxatives and have several biological effects. Long-term use of AQ laxatives is associated with an increased risk of serious adverse events (AEs), such as colorectal cancer (CRC). We will systematically synthesize the evidence on the potential association between the use of AQ laxatives and the risk of CRC.

Methods and analysis: We will search MEDLINE, Embase, Scopus, the Cochrane Library, Google Scholar and Clinicaltrials.gov, for clinical trials and observational studies performed on subjects taking AQ laxatives, assessing the incident of CRC. To avoid missing any relevant studies, we will search the bibliographies of retrieved papers and recent reviews in the field. Interventions will include products containing oral AQ laxatives, in particular those derived from rhubarb, senna, cascara, buckhorn, and aloe. Two review authors will independently screen title, abstract and full texts, and will independently extract data from included studies. The primary outcome is the number of subjects diagnosed with CRC, while the secondary outcome will be cases of melanosis coli. We will also consider all other AEs reported in the included studies, in particular: intestinal bleeding, alterations of gastrointestinal motility, and potential for dependence. When possible and appropriate, for each outcome a meta-analysis will be performed.

Discussion: This protocol is prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines. The protocol gives an insight into the scope and parameters for the systematic review to be carried out.
Systematic review registration: The protocol is registered in international prospective register of systematic reviews (PROSPERO), ID = CRD42019125414.”