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Risks and benefits of antioxidant dietary supplement use during cancer treatment: Protocol for a scoping review

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ABSTRACT

Introduction: Antioxidant dietary supplements are used by many cancer patients to reduce the side effects of chemotherapy and improve prognosis. While some research indicates oral antioxidant supplementation reduces side effects and improves patient survival, other studies suggest the use of antioxidant dietary supplements may interfere with chemotherapy and reduce its curative effects. There is a need to clarify the evidence base on the impact of dietary antioxidant supplementation during chemotherapy on both side effect and treatment efficacy outcomes. We will use a scoping review approach to identify what systematic review evidence exists regarding beneficial and harmful effects of dietary antioxidant supplements when used during cancer treatment.

Methods and analysis: We will use Arksey & O'Malley and Joanna Briggs Institute methods for scoping reviews. We will systematically search PubMed, Embase, CINAHL, Scopus, Dissertations & Theses Global, and the Cochrane Library from inception to October 2020. Systematic reviews of randomized controlled trials of oral dietary antioxidant supplements used by participants receiving curative chemotherapy, radiotherapy, or other biological therapy for cancer will be eligible. Two reviewers will screen citations and full texts for inclusion and chart data on research questions from included reviews. Two reviewers will assess the overall confidence in systematic review results using AMSTAR-2, and summarized evidence will focus on reviews rated at high or moderate overall confidence. Tables will be used to map existing evidence and identify evidence gaps for safety and effectiveness outcomes.

Ethics and dissemination: This scoping review does not require ethical approval as it is a secondary assessment of available literature. The results will be presented at conferences and submitted for publication in a peer-reviewed journal. We will also disseminate results to

community and clinical stakeholders and involve them in developing subsequent research to address critical existing gaps in the evidence as identified by the scoping review.

ARTICLE SUMMARY

Strengths and limitations of this study

- This will be the first scoping review to provide an up-to-date overview of the available systematic review literature on the potential benefits and harms of antioxidant dietary supplement use during curative treatment for cancer.
- The review will incorporate a focus on understanding whether there is a relationship between use of antioxidant dietary supplements and the therapeutic efficacy of chemotherapy.
- The review will use the AMSTAR-2 tool to distinguish between systematic reviews providing different levels of certainty for results and emphasize reviews at overall high or moderate certainty.
- Results from this scoping review will be used to further the understanding of the breadth of antioxidant dietary supplement interventions and their effects during chemotherapy and to identify current gaps in knowledge.

INTRODUCTION

Cancer is the second leading cause of death in the United States,[1] having a significant deleterious impact on individual patients and society at large. Approximately 1 in 2 men and 1 in 3 women will develop cancer in their lifetime.[2] Cancer treatment is a broad area of research, as cancer is a complex, dynamic set of diseases, requiring newer technologies and innovative treatments with fewer adverse effects. Conventional medical therapies for those with cancer include but are not limited to chemotherapy and radiotherapy, both of which are associated with potentially debilitating side effects and reduced quality of life.[3]

Chemotherapy is a treatment approach designed to stop cancer growth either by preventing the reproduction of new cancer cells or killing cancer cells directly. Most chemotherapy drugs target the cell cycle, by altering or damaging deoxyribonucleic acid (DNA) in the cell.[4] One of the most significant causes of oxidative stress and inflammation is related to DNA damage.[5] Additionally, anti-cancer drugs cannot distinguish between cancer cells and healthy cells, which is thought to be a reason for chemotherapy's negative side effects.[4, 6] A majority of patients receiving chemotherapy report at least one side effect from the drug, most notably fatigue, nausea, vomiting, diarrhea, pain, rash, constipation, and shortness of breath.[6] For this reason, patients receiving cancer treatment often seek complementary and alternative adjuvant therapies to reduce side effects and improve quality of life.

A popular group of complementary therapies used by cancer patients is antioxidants, which can be administered through dietary interventions, intravenous infusion, or most commonly, dietary supplementation.[7] Antioxidants are substances that act to prevent or delay cellular damage, notably by stabilizing free radicals and reducing oxidative stress. The observation in laboratory studies that antioxidants decrease oxidative stress has made the use of antioxidants

common, albeit somewhat controversial, in the attempt to prevent or treat chronic disease.[8] Commonly used antioxidants include vitamins, minerals, phytochemicals and other related substances, and amino acids.[9]

While antioxidant supplements are popular among the general public, the evidence on antioxidant supplementation to prevent chronic disease or improve health outcomes is equivocal.[10-12] Although there is an increased willingness of medical professionals to use complementary therapies, the belief persists among many providers that alternative therapies could harm patients.[13-15] When patients use over the counter (OTC)dietary supplements without informing their physician, this may increase risk of interactions with prescription medications and undermine the patient-provider relationship.[16, 17]

A 2016 overview concluded that antioxidant supplementation reduces adverse effects and chemotoxicities from chemotherapy, though the authors noted inconsistencies in the literature.[9] The most studied oral antioxidant supplement may be melatonin, shown in vitro to have anti-tumor activity when used with irradiation.[18] However, while some research suggests that oral antioxidant supplementation during chemotherapy may increase patient survival, other research suggests that it may diminish the efficacy of the chemotherapeutic treatment.[19, 20] There is concern that antioxidant therapies may interact with the cytotoxic effects of chemotherapy, lessening adverse side effects and improving quality of life, but also rendering the cancer treatment less effective.[21] For example, a recently published secondary data analysis from a clinical trial comparing chemotherapy schedules in breast cancer identified an increased hazard of recurrence in women using antioxidant supplements both before and during chemotherapy.[22]

We are aware of many studies over the past twenty years that discuss dietary supplements during cancer treatment; several of these are systematic reviews.[9, 23-29] However, most

systematic reviews focus on the potential reduction in chemotherapy side effects with supplements. We are not aware of a review systematically collecting evidence on the relationship between antioxidant supplements and therapeutic response to chemotherapy, with the exception of one review conducted more than 10 years ago.[30] Since publication of that review, there have been changes in chemotherapy regimens and antioxidant use patterns, and more current systematic reviews may have captured but not highlighted relevant information on response to chemotherapy. There is, therefore, a need to systematically identify the best currently available evidence on this topic. Currently, there is no comprehensive overview of the literature outlining the benefits and harms of antioxidant supplements for patients receiving conventional cancer therapies, and evidence appears particularly scant on the question of whether antioxidant supplementation may negatively interact or interfere with chemotherapeutic treatment. This paucity of evidence precludes the ability to make evidence-based recommendations on use of antioxidant supplements by cancer patients.

We will use scoping review methodology to identify and compile the data from previous systematic reviews of randomized controlled trials (RCTs) regarding not only the reduction of chemotherapy side-effects but also the efficacy of chemotherapy when oral antioxidant supplements are used in conjunction by persons with cancer. A scoping review is a form of knowledge synthesis that 'aims to map key concepts, types of evidence, and gaps in a defined area or field by systematically searching, selecting, and charting available evidence.'[31] Extracting information from systematic reviews will allow us to identify what is known and where there remain knowledge gaps on the topic. Specifically, this paper is focused on identifying 1) to what extent previous systematic reviews of RCTs have assessed the efficacy of chemotherapy in the presence of adjuvant antioxidant supplementation, and 2) what is known from systematic reviews

of RCTs on the potential benefits and harms of adjuvant antioxidant supplementation during chemotherapy for cancer, including relationships between supplementation and the efficacy of chemotherapy. The results will inform future cancer research activities in this area.

METHODS

This protocol follows the Joanna Briggs Institute (JBI) guidance on protocols for scoping reviews and has been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist.[32, 33] The completed scoping review will be reported in accordance with the PRISMA extension for scoping reviews (PRISMA-ScR).[32]

We will follow the Arksey and O'Malley scoping review framework, modified by Levac 2010 and JBI (2017 and 2020),[34-38] consisting of the following steps:

(1) Identifying the research question;

(2) Identifying relevant studies;

(3) Selecting studies for inclusion;

(4) Charting data from included studies;

(5) Collating, summarizing and reporting the results;

(6) Consultation (optional, included).

Step 1: Identifying the research question

The areas of uncertainty concerning the use of antioxidant supplements during chemotherapy for cancer have been described above. We will answer the following research questions:

1) Among systematic reviews of RCTs on antioxidant supplements during chemotherapy, to what extent have research questions been posed regarding the effects of antioxidant supplementation on the therapeutic efficacy of chemotherapy?

2) What systematic review evidence exists regarding the use of antioxidant dietary supplements during chemotherapy with respect to:

a) whether supplementation with specific antioxidants promotes or attenuates the efficacy of chemotherapeutic treatment?

b) improvement of chemotherapy-related side effects and quality of life? and

c) adverse clinical effects potentially associated with antioxidant supplementation?

Step 2: Identifying relevant studies

Types of evidence sources

The types of evidence of interest for this scoping review will be systematic reviews of RCTs. This is the most efficient way to identify comprehensive evaluations of available high-quality evidence. For the purposes of this scoping review, we will define systematic reviews of RCTs as reviews that: 1) have a clear research question; 2) specify eligibility criteria for including studies; 3) seek to comprehensively identify RCTs relevant to the research question; 4) report the critical appraisal (e.g., risk of bias) of the included RCTs; and 5) present a synthesis, either quantitative or qualitative, of the characteristics and findings of the RCTs.[39] We will include systematic reviews focused on efficacy, effectiveness, or safety. While the current approach focuses on evidence from systematic reviews of RCTs, we will not exclude reviews that also seek to identify additional sources of evidence (e.g., observational studies). Furthermore, narrative (non-systematic) reviews addressing our outcomes of interest will be excluded initially but may be given secondary consideration dependent upon the quantity of systematic reviews identified. We will include both published and unpublished systematic reviews but will exclude those reported solely as conference abstracts because they generally contain limited information. We will not exclude systematic reviews on the basis of language or date of publication.

Data sources and search for studies

The initial search strategy was developed by an experienced medical information specialist (EFG) in collaboration with the remainder of the review team. The search strategy will be finalized after peer-review by another experienced medical information specialist using the PRESS Peer Review of Electronic Search Strategies.[40] Databases searched from inception will include PubMed (Pubmed.gov), Embase (Embase.com), CINAHL (EBSCOhost), Scopus (Scopus.com), Dissertations & Theses Global (ProQuest), and the Cochrane Library (WileyOnline). A combination of keywords and subject headings will be adapted for use according to the specifications of each database. All records retrieved will include at least one antioxidant-related term and a term related to cancer therapies. Examples of antioxidant terms include but are not limited to vitamin C, lycopene, and melatonin. Cancer therapy terms include but are not limited to chemotherapy, radiotherapy, antineoplastic, and anticancer. The initial search strategy for Embase is reported in Appendix 1. In addition to screening records retrieved from searching bibliographic databases, we will search the PROSPERO database of registered systematic reviews, scan the reference lists of included reviews and contact experts in the field to identify additional relevant systematic reviews.

Step 3: Selecting studies for inclusion

We will use the PCC (Population, Concepts and Context) framework to implement eligibility criteria for included studies.[38]

Population

Participants with cancer who are receiving chemotherapy, radiotherapy, or other biological therapy for treatment of cancer will be sought. There will be no restrictions by population characteristics (e.g., sex, age, comorbidities, geographic location), or type or stage of cancer.

Concepts

The core intervention of interest is antioxidant dietary supplements concomitant with chemotherapy, radiotherapy, or other biological therapy for cancer. We are defining antioxidant dietary supplements as orally-consumed products with known ability to prevent cellular damage by reacting with oxidizing free radicals.[41] Antioxidant dietary supplements cover a wide range of substances, including vitamins (e.g. vitamin C), minerals (e.g. selenium), amino acids (e.g. n-acetylcysteine), carotenoids (e.g. lycopene), botanicals (e.g. polyphenols), and hormones (e.g. melatonin). Studies involving IV administration of antioxidants in a medical setting (e.g., IV vitamin C) will be excluded from this scoping review. Oral and IV antioxidants are not only processed differently by the body but oral supplements may be taken by patients without direct assistance of medical professionals, and thus have different clinical and public health implications. Studies involving mushrooms and mushroom products will be excluded because their mechanism is primarily through immunomodulation.[42] Studies involving compound herbal formulas will also be excluded due to the potential for multiple mechanisms of activity that confound the research question. Finally, although many foods such as fruits and vegetables are good sources of antioxidants, whole food dietary interventions (e.g., changes in food habits) will also be excluded from this scoping review due to the potential for confounding by non-antioxidant dietary components with known activity against cancer (e.g., histone deacetylase (HDAC)-inhibition, DNA methylation).[43, 44]

The core outcomes of interest will consist of 1) therapeutic response to treatment with chemotherapy, radiotherapy, or other biological therapy, 2) improvements in chemotherapy-related side effects and quality of life, and 3) increases in adverse effects potentially related to antioxidant supplementation. Response to treatment may be measured as mortality or with

indicators of morbidity (e.g., cancer progression, recurrence). Because it may not be possible to establish whether side effects and other adverse events are more likely related to the cancer treatment or to the supplement use, we will document when adverse events are presented within the reviews as side effects due to either cancer treatment or supplement use, but we will discuss the findings both separately and jointly. We will include outcomes measured at any time point.

Context

The context is cancer treatment with curative intent. The palliative use of chemotherapy, radiotherapy, or other biological therapies will be excluded because a core aspect of this scoping review is the evaluation of the evidence on antioxidant supplements with regard to possible interference with the curative objectives of treatment. We will not restrict context by date, healthcare setting or country.

Data management

Citations for retrieved records will be downloaded into EndNote X8 and deduplicated. Citations will then be uploaded to Covidence and screened for inclusion in two stages.[45] At the first stage, two team members will independently screen all records for relevance on the basis of record title and abstract. Prior to title and abstract screening, the team members will carry out a pilot screening of randomly selected records, to ensure that they understand and agree upon the initial inclusion criteria. During the title and abstract screening, discrepancies between screeners will regularly be resolved, to prevent development and continuation of differing interpretations of the inclusion criteria.[46] All records that are deemed to be potentially relevant to the scoping review will progress to full text screening. Once records are ready for full text screening, a calibration exercise will be performed in which all team members screen a set of the same randomly selected 25 records against the inclusion and exclusion criteria for the review. The results

of this screening will be compared between team members, and any necessary clarifications to the inclusion and exclusion criteria, or modifications of those criteria, will be made and documented in the completed scoping review. After any clarification or modification of the selection criteria, and agreement among the team on the results of the calibration exercise, two team members will independently screen each full text record for inclusion. Discrepancies between screeners will be resolved by discussion or involvement of a third team member. The study citation and brief reason for exclusion will be provided for each excluded record and a flow chart of the screening process will be provided in accordance with PRISMA-ScR.

Step 4: Charting data from included studies

Data will be extracted from each included systematic review. These data will include bibliographic information (e.g., authors, date of publication, journal of publication), information on the methods (e.g. the research question, study enrollment criteria and design), information on results, and the key findings for each included review. See Appendix 2 for a draft of the data charting form displaying the elements to be extracted from each review. To ensure that the data charting form is comprehensive and clear, we will pilot test the form prior to embarking on the full data extraction. Three members of the author team will use the form to chart data from the same three reviews and compare the extracted information across authors. Anything that is unclear or missing from the data charting form will be discussed and clarifications and modifications will be addressed in collaboration with the full author team until all authors are satisfied that the data charting form is suitable for extraction of all relevant results. Data extraction will then be carried out for each study by one author and verified by a second author.

Quality Assessment

Methodological shortcomings in the conduct of systematic reviews may lead to incomplete and biased findings and reduce our confidence in review conclusions. Therefore, in addition to extracting key data from all systematic reviews, we will carry out and report an assessment of the conduct of each of the included systematic reviews, using the updated version of AMSTAR (A Measurement Tool to Assess Systematic Reviews) (AMSTAR-2).[47] AMSTAR-2 is a critical appraisal tool for systematic review conduct that can be used to assess the overall confidence in systematic review results at one of four levels: high, moderate, low, and critically low. The interpretation of an overall high level of confidence is that "the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest," while the interpretation of an overall low level of confidence is that "the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest."[47] See Appendix 3 for the AMSTAR-2 rating criteria, rubric, and interpretation for overall assessment of confidence in review results. AMSTAR-2 assessment will be carried out for each study by one author and verified by a second author.

Although critical assessment of the evidence is optional for scoping reviews, we wish to focus on available systematic review evidence in which we can have confidence. We will therefore focus our presentation on systematic reviews rated as at overall moderate or high level of confidence with AMSTAR-2. We will highlight the charted data extracted from these reviews, and we may also extract additional data, using the methods described above to develop and pilot an additional data charting form, to capture further details on the findings of these reviews.

Step 5: Collating, summarizing and reporting the results

As scoping reviews do not formally synthesize the evidence, this review will provide a descriptive summary of the evidence by calculating frequencies for data elements and mapping this evidence against the objectives of the review. For example, we will identify evidence on individual antioxidants with regard to the questions of interest from each review, indicating the underlying populations (types and stages of cancer, chemotherapeutic regimens) the evidence is sourced from, and the AMSTAR-2 rating of the reviews providing this information. Results will be presented in tables and charts. We will conclude by discussing whether we believe there is reliable systematic review evidence on the potential benefits and risks of antioxidant supplements during chemotherapy and suggesting potential avenues for further research.

Step 6: Consultation

As described under the Data sources and search for studies, we will consult experts in the field to identify additional systematic reviews not found through database searching. We will also consult with stakeholders in cancer treatment (e.g., clinicians, patients) to inform the elements to be included in the data charting. Through consultation with these stakeholders we will ensure that relevant characteristics of the populations, interventions, and outcomes are captured and important gaps in the evidence may be identified. In keeping with best practices in community-engaged research, we will disseminate the findings of the review to community stakeholders and patients. Community engagement will also be used to inform recommendations for future research based on the review.

Ethics and dissemination

This scoping review does not require ethics approval as it is a secondary review of the literature. Based upon the results of this review, we will disseminate our findings of both reliable evidence (where it exists) or a gap in reliable evidence and a need for additional research. This

dissemination will be carried out through presentations at relevant conferences and publication in a peer-reviewed open-access journal. As mentioned above, we will also disseminate the findings to community and patient stakeholders. We will ask these stakeholders to join with clinical and research stakeholders to identify the best ways to address any critical existing gaps in the evidence (e.g., a focused systematic review, further randomized trials) and prioritize the next steps.

Patient and public involvement

As described above, we will consult with patients to inform the development of data charting. We will also engage with patients, clinicians and other stakeholders to disseminate summaries of the review findings in appropriate formats and venues. Finally, we will involve patients and the public in developing and prioritizing future research activities based upon the findings of this project.

DISCUSSION

Implications

We will use the findings from this review to develop to develop future research priorities and initiatives to help fill remaining critical gaps in the current literature and contribute to key next steps. We will then work with patients and clinicians to prioritize evidence needs, and consult with clinical, research, and patient stakeholders on the most appropriate methods (e.g., new or updated systematic reviews versus additional primary studies) for addressing these gaps. Near the end of the scoping review process, when we are able to characterize the extent of available reliable evidence, we will begin to formalize partners and processes for these next steps.

Potential limitations and mitigation strategies

Though scoping the entirety of observational and clinical evidence on this topic is beyond the scope of the current initiative, we believe that focusing on systematic reviews is the most

efficient way to characterize the weight of the current research evidence. We are also uncertain about the volume of review evidence, which makes it difficult to plan ahead for either superficial or very detailed data extraction. The iterative nature of scoping reviews allows us to be flexible in response to the quantity and quality of the evidence and prioritize summarizing evidence according to characteristics such as review quality or recency. Regular engagement with clinical and research partners during the conduct of the scoping review will allow us to modify our methods in such a way as to develop summaries of review evidence that are maximally relevant and useful to inform practice. We plan to ensure the transparency of our methods by devoting a section of the final publication to changes from and refinements to this protocol, together with the rationale for any revisions. At the conclusion of this project we will develop a plan, including potential future funding applications, for the next steps in a research agenda to inform decisions by patients and providers on the potential benefits or harms of dietary antioxidant supplementation during chemotherapy.

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Author Contributions: AE, CLK, and CD jointly conceived the study and developed the research questions. LSW proposed the scoping review methodology and developed the protocol with IM and SS. EFG developed the search strategy. LSW drafted the manuscript. All authors revised the manuscript and approved the final text. LSW is guarantor of the review.

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APPENDIX 1 – EMBASE PRELIMINARY SEARCH STRATEGY

Embase (Embase.com) – 7253 references retrieved on 06 October 2020

One-line search run in Results tab of Embase.com platform:

('antioxidant'/exp OR antioxidant*:ti,ab,kw OR 'anti-oxidant*':ti,ab,kw OR antioxidat*:ti,ab,kw OR 'anti-oxidat*':ti,ab,kw OR 'antioxidant activity'/exp OR 'acetylcysteine'/exp OR acetylcystein*:ti,ab,kw OR 'acetyl cysteine':ti,ab,kw OR acetadote:ti,ab,kw OR mucomyst:ti,ab,kw OR cetylev:ti,ab,kw OR 'arginine'/exp OR arginin*:ti,ab,kw OR 'ascorbic acid'/exp OR 'ascorbic acid*':ti,ab,kw OR 'vitamin c':ti,ab,kw OR ascorbate:ti,ab,kw OR 'ascorbyl palmitate':ti,ab,kw OR 'carotenoid'/exp OR caroten*:ti,ab,kw OR 'coumarin'/exp OR coumarin*:ti,ab,kw OR cumarin*:ti,ab,kw OR 'curcumin'/exp OR curcumin*:ti,ab,kw OR turmeric:ti,ab,kw OR 'ellagic acid'/exp OR 'ellagic acid*':ti,ab,kw OR 'benzoanic acid*':ti,ab,kw OR 'benzoaric acid*':ti,ab,kw OR 'melatonin'/exp OR melatonin*:ti,ab,kw OR circadin:ti,ab,kw OR 'polyphenol'/exp OR polyphenol*:ti,ab,kw OR 'retinol'/exp OR retinol:ti,ab,kw OR 'vitamin a':ti,ab,kw OR 'retinyl palmitate':ti,ab,kw OR 'retinoic acid*':ti,ab,kw OR 'selenium'/exp OR selenium:ti,ab,kw OR selenicum:ti,ab,kw OR 'tocopherol'/exp OR tocopherol*:ti,ab,kw OR tocoferol:ti,ab,kw OR 'vitamin e':ti,ab,kw OR 'ubiquinone'/exp OR ubiquinone:ti,ab,kw OR 'vitamin q':ti,ab,kw OR 'coenzyme q10':ti,ab,kw OR coq10:ti,ab,kw OR 'coenzyme q':ti,ab,kw OR 'zinc'/exp OR zinc:ti,ab,kw OR zincum:ti,ab,kw OR 'thioctic acid'/exp OR 'thioctic acid*':ti,ab,kw OR 'lipoic acid*':ti,ab,kw OR 'resveratrol'/exp OR resveratrol:ti,ab,kw OR 'glutathione'/exp OR glutathione:ti,ab,kw OR glutathiol:ti,ab,kw OR 'chlorogenic acid'/exp OR 'chlorogenic acid*':ti,ab,kw OR 'ferulic acid'/exp OR 'ferulic acid*':ti,ab,kw OR 'ferulate sodium':ti,ab,kw OR 'sodium ferulate':ti,ab,kw OR 'lycopene'/exp OR lycopene:ti,ab,kw OR

'docosahexaenoic acid'/exp OR docosahexaeno*:ti,ab,kw OR 'icosapentaenoic acid'/exp OR 'icosapentaenoic acid*':ti,ab,kw OR 'eicosapentaenoic acid*':ti,ab,kw OR 'vitamin supplementation'/exp OR 'vitamin supplement*':ti,ab,kw OR 'hibiscus'/exp OR hibiscus:ti,ab,kw OR 'folic acid'/exp OR 'folic acid*':ti,ab,kw OR folate:ti,ab,kw OR 'catechin'/exp OR catechin*:ti,ab,kw OR 'catechuic acid*':ti,ab,kw OR ciandiol:ti,ab,kw OR 'anthocyanidin'/exp OR anthocyanidin:ti,ab,kw OR 'tannin'/exp OR tannin*:ti,ab,kw OR 'tannic acid*':ti,ab,kw OR gallotanni*:ti,ab,kw OR 'rutoside'/exp OR rutoside:ti,ab,kw OR rutin:ti,ab,kw OR rutinoside:ti,ab,kw OR 'vitamin p':ti,ab,kw OR 'isoflavone'/exp OR isoflavone*:ti,ab,kw OR 'quercetin'/exp OR quercetin*:ti,ab,kw OR quercitin*:ti,ab,kw OR quercetol*:ti,ab,kw OR 'lignan'/exp OR lignan*:ti,ab,kw OR 'allicin'/exp OR allicin:ti,ab,kw OR '5 methoxytryptamine'/exp OR methoxytryptamine:ti,ab,kw OR mexamine:ti,ab,kw OR 'uric acid'/exp OR 'uric acid*':ti,ab,kw OR 'urobilinogen'/exp OR urobilinogen:ti,ab,kw OR urinobilinogen:ti,ab,kw OR 'melanoidin'/exp OR melanoidin:ti,ab,kw OR 'phytic acid'/exp OR 'phytic acid*':ti,ab,kw OR 'phytinic acid*':ti,ab,kw OR 'saponin'/exp OR saponin*:ti,ab,kw OR glycosaponin*:ti,ab,kw OR 'methionine'/exp OR methionin*:ti,ab,kw OR levomethionine:ti,ab,kw OR methiolate:ti,ab,kw OR 'albumin'/exp OR albumin:ti,ab,kw OR albumen:ti,ab,kw OR 'lactoferrin'/exp OR lactoferrin*:ti,ab,kw OR lactotransferrin*:ti,ab,kw OR 'chromium'/exp OR chromium:ti,ab,kw OR 'transferrin'/exp OR transferrin*:ti,ab,kw OR siderophilin:ti,ab,kw OR 'ferritin'/exp OR ferritin*:ti,ab,kw OR immunoferritin:ti,ab,kw OR 'manganese'/exp OR manganese:ti,ab,kw OR cutaval:ti,ab,kw OR 'molybdenum'/exp OR molybden*:ti,ab,kw OR 'fish oil'/exp OR 'fish oil*':ti,ab,kw OR promega:ti,ab,kw OR 'omega 3 fatty acid'/exp OR 'omega 3 fatty acid*':ti,ab,kw OR 'omega 3 carboxylic acid*':ti,ab,kw OR 'alternative medicine'/de OR 'alternative medicine*':ti,ab,kw OR 'complementary

medicine*':ti,ab,kw OR 'complementary therap*':ti,ab,kw OR 'diet supplementation'/exp OR 'diet* supplement*':ti,ab,kw) AND ('chemotherapy'/exp OR chemotherap*:ti,ab,kw OR 'radiotherapy'/exp OR radiotherap*:ti,ab,kw OR 'cancer therapy'/exp OR (((cancer OR radiation OR irradiation OR tumor* OR tumour* OR neoplas* OR oncolog*) NEAR/3 (therap* OR treat* OR inhibit*)):ti,ab,kw) OR 'adjuvant radiotherapy'/exp OR 'antineoplastic agent'/exp OR anticancer*:ti,ab,kw OR 'anti-cancer*':ti,ab,kw OR anticarcinogen*:ti,ab,kw OR 'anti-carcinogen*':ti,ab,kw OR 'antineoplastic activity'/exp OR antineoplastic*:ti,ab,kw OR 'anti-neoplastic*':ti,ab,kw OR antitumor:ti,ab,kw OR 'anti-tumor':ti,ab,kw OR antitumour:ti,ab,kw OR 'anti-tumour':ti,ab,kw OR 'chemoradiotherapy'/exp OR chemoradiotherap*:ti,ab,kw OR 'alkylating agent*':ti,ab,kw OR alkylator*:ti,ab,kw OR 'antimetabolite'/exp OR antimetaboli*:ti,ab,kw OR ‘anti-metaboli*’:ti,ab,kw OR 'antimitotic agent'/exp OR antimitotic*:ti,ab,kw OR 'anti-mitotic*':ti,ab,kw OR 'mitotic inhibitor*':ti,ab,kw OR 'mitosis inhibitor*':ti,ab,kw OR 'anthracycline'/exp OR anthracyclin*:ti,ab,kw OR 'protein tyrosine kinase inhibitor'/exp OR 'tyrosine kinase inhibitor*':ti,ab,kw OR tki:ti,ab,kw OR 'tyrosine protein kinase inhibitor*':ti,ab,kw OR 'protein serine threonine kinase inhibitor'/exp OR 'serine threonine kinase inhibitor*':ti,ab,kw OR 'checkpoint inhibitor'/exp OR 'checkpoint inhibitor*':ti,ab,kw OR 'anti pd1':ti,ab,kw OR 'anti pdl1':ti,ab,kw OR 'antimyeloma activity'/exp OR antimyeloma*:ti,ab,kw OR 'anti-myeloma*':ti,ab,kw OR 'dna topoisomerase inhibitor'/exp OR 'topoisomerase inhibitor*':ti,ab,kw OR 'topoisomerase 1 inhibitor*':ti,ab,kw OR 'topoisomerase i inhibitor*':ti,ab,kw OR 'antiandrogen'/exp OR 'antiandrogen therapy'/exp OR 'anti-androgen*':ti,ab,kw OR antiandrogen*:ti,ab,kw OR 'androgen antagonist*':ti,ab,kw OR 'antiestrogen'/exp OR 'anti-estrogen*':ti,ab,kw OR 'anti-oestrogen*':ti,ab,kw OR antiestrogen*:ti,ab,kw OR antioestrogen*:ti,ab,kw OR 'estrogen antagonist*':ti,ab,kw OR

'oestrogen antagonist*':ti,ab,kw OR 'cancer hormone therapy'/exp OR 'cancer hormone therap*':ti,ab,kw OR 'cancer patient'/exp OR 'cancer patient*':ti,ab,kw OR 'oncolog* patient*':ti,ab,kw OR electrochemotherap*:ti,ab,kw OR photochemotherap*:ti,ab,kw OR chemoembolization:ti,ab,kw OR chemoembolisation:ti,ab,kw OR carcinochemotherap*:ti,ab,kw OR multichemotherap*:ti,ab,kw OR polychemotherap*:ti,ab,kw OR antileukemi*:ti,ab,kw OR 'anti-leukemi*':ti,ab,kw OR antileukaemi*:ti,ab,kw OR 'anti-leukaemi*':ti,ab,kw OR antimetasta*:ti,ab,kw OR 'anti-metasta*':ti,ab,kw OR antimutagen*:ti,ab,kw OR 'anti-mutagen*':ti,ab,kw) AND (metaanaly*:ti,ab,kw OR 'met analy*':ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR (((systematic* OR methodologic* OR collaborative OR integrative) NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((pool* NEAR/3 analy*):ti,ab,kw) OR handsearch*:ti,ab,kw OR 'hand search*':ti,ab,kw OR 'data synthes*':ti,ab,kw OR 'data extraction*':ti,ab,kw OR 'data abstraction*':ti,ab,kw OR metaregression*:ti,ab,kw OR 'meta regression*':ti,ab,kw OR [cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

APPENDIX 2 – DRAFT ELEMENTS FOR DATA CHARTING

Bibliographic characteristics

Journal name
Year of publication
Country of corresponding author
Funding

Review question and methods

Review protocol cited/provided
Inclusion criteria for participants: types of cancer(s), stage, other disease characteristics
Inclusion criteria for participants: age, sex, other demographic characteristics
Inclusion criteria for participants: cancer treatment(s)
Inclusion criteria for interventions: specific supplements or categories of supplements
Inclusion criteria for comparators:
Outcomes sought from included studies (including not only domain but also instrument or scale and time frame if specified): [may break down by type eg, quality of life, adverse effect, success of cancer treatment]
Study designs eligible for inclusion:
List of databases searched
Total number of databases searched
Date of last database search
Quality assessment tool
Planned meta-analyses, subgroup analyses and sensitivity analyses

Planned methods to assess the quality/certainty of effect estimate

Review results and analyses from included* RCTs

Number of included RCTs
Number of participants in included RCTs
Age, sex, other demographic characteristics of participants in included RCTs
Cancer characteristics of participants in included RCTs
Cancer treatment(s) provided to participants in included RCTs
Antioxidant interventions in included RCTs
Comparators in included RCTs:
Outcomes present in included RCTs:
List of meta-analyses conducted
List of subgroup analyses conducted
List of sensitivity analyses conducted

*all references to included studies refer to those studies assessing effects of oral antioxidant supplement interventions during curative treatment for cancer; systematic reviews may have a broader scope.

For each review, results for each antioxidant-related PICO question

Participant/Intervention/Comparator/Outcome/Time (may group multiple time points)
Are any results presented?
If so, were results qualitative or quantitative?
If quantitative, what was the effect estimate?
Quote or summary of author assessment of findings on the PICO question

Certainty/quality of evidence for the results (if assessed by authors)
Confidence in results of the review (see AMSTAR 2 assessment)

APPENDIX 3 – AMSTAR-2 CRITERIA FOR CONFIDENCE IN THE RESULTS OF SYSTEMATIC REVIEWS

AMSTAR-2 criteria [47]
1. Did the research questions and inclusion criteria for the review include the components of PICO? (Y, N)
2. Did the report of the review contain explicit statement that the review methods were established prior to conduct of the review? (Y, PY, N)
3. Did the review authors explain their selection of the study designs for inclusion in the review? (Y, N)
4. Did the reviewer authors use a comprehensive literature search strategy? (Y, PY, N) CRITICAL FLAW if not Y, PY
5. Did the review authors perform study selection in duplicate? (Y, N)
6. Did the review authors perform data extraction in duplicate? (Y, N)
7. Did the review authors provide a list of excluded studies and justify the exclusions? (Y, PY, N)
8. Did the review authors describe the included studies in adequate detail? (Y, PY, N)
9A. RCTS- Did authors use a satisfactory technique for assessing the risk of bias (ROB) in individual studies that were included in the review? (Y, PY, N, NA- includes only NRSI) CRITICAL FLAW if not Y, PY
9B. NRSI- Did authors use a satisfactory technique for assessing the risk of bias (ROB) in individual studies that were included in the review? (Y, PY, N, NA- includes only RCTs) CRITICAL FLAW if not Y, PY

10. Did the review authors report on the sources of funding for the included studies? (Y, N)
11A. RCTs- If meta-analysis was performed did the authors use appropriate methods for statistical combination of results? (Y,N, only NRSI, No MA) CRITICAL FLAW if not Y, PY
11B. NRSI- If meta-analysis was performed did the authors use appropriate methods for statistical combination of results? (Y,N, only RCTs, no MA) CRITICAL FLAW if not Y, PY
12. If meta-analysis was performed, did the review authors assess the potential impact of ROB in individual studies on the results of the meta-analysis or other evidence synthesis? (Y, N, No MA, No QA)
13. Did the review authors account for ROB in individual studies when interpreting/discussing the results of the review? (Y, N, No QA) CRITICAL FLAW if not Y, PY
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (Y, N)
15. Did the review authors carry out an adequate investigation of publication bias, and discuss its likely impact on the results of the review? (Y, N)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for the review? (Y, N)
Number of critical flaws (critical items answered N):
Number of non-critical flaws (non-critical items answered N):
Rubric for overall confidence: High confidence: no critical flaws with zero or one non-critical flaw.

Moderate confidence: no critical flaws with > 1 non-critical flaw. Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence Low confidence: one critical flaw with or without any non-critical flaws Critically low confidence: more than one 1 critical flaw with or without any non-critical flaws.
Overall confidence in the results of the review (High/Moderate/Low/Critically Low):
Interpretation of quality levels: High: The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. Moderate: The systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review Low: The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest Critically Low: The review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	pg 1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A not an update
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A not registered as PROSPERO does not register scoping reviews
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	pg 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	pg. 18

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A not an amendment
Support			
Sources	#5a	Indicate sources of financial or other support for the review	pg. 18
Sponsor	#5b	Provide name for the review funder and / or sponsor	pg. 18
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	pg. 18
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	pg 5-8
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	pg 7-9
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	pg 9-12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	pg 10
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	pg 12

Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	pg 12-13
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	pg 13
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	pg 13-14, Appendix 2
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	pg 13-14, Appendix 2
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	pg 14, Appendix 3
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	N/A no quantitative synthesis planned
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	N/A no quantitative synthesis planned
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A no quantitative synthesis planned
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	pg 15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A no quantitative synthesis planned
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A individual reviews to be scoped but body of

evidence evidence not assessed for confidence

Notes:

- 1b: N/A not an update
- 2: N/A not registered as PROSPERO does not register scoping reviews
- 4: N/A not an amendment
- 12: pg 13-14, Appendix 2
- 13: pg 13-14, Appendix 2
- 14: pg 14, Appendix 3
- 15a: N/A no quantitative synthesis planned
- 15b: N/A no quantitative synthesis planned
- 15c: N/A no quantitative synthesis planned
- 16: N/A no quantitative synthesis planned
- 17: N/A individual reviews to be scoped but body of evidence not assessed for confidence This checklist was completed on 19. November 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Risks and benefits of antioxidant dietary supplement use during cancer treatment: Protocol for a scoping review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-047200.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Feb-2021
Complete List of Authors:	Wieland, L. Susan; University of Maryland School of Medicine, Center for Integrative Medicine Moffet, Ilana; University of Michigan College of Literature Science and the Arts Shade, Sydney; Geisinger Commonwealth School of Medicine Emadi, Ashkan ; University of Maryland Baltimore, School of medicine; University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center Knott, Cheryl; University System of Maryland, Department of Behavioral and Community Health; University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Community Outreach and Engagement Gorman, Emily; University of Maryland Baltimore, Health Sciences and Human Services Library D'Adamo, Christopher ; University of Maryland School of Medicine, Center for Integrative Medicine
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Complementary medicine
Keywords:	CHEMOTHERAPY, COMPLEMENTARY MEDICINE, ONCOLOGY

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Risks and benefits of antioxidant dietary supplement use during cancer treatment: Protocol for a scoping review

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Keywords: Dietary supplements, Antioxidants, Neoplasms, Chemotherapy

Word count: 4156

ABSTRACT

Introduction: Antioxidant dietary supplements are used by many cancer patients to reduce the side effects of chemotherapy and improve prognosis. While some research indicates oral antioxidant supplementation reduces side effects and improves patient survival, other studies suggest the use of antioxidant dietary supplements may interfere with chemotherapy and reduce its curative effects. There is a need to clarify the evidence base on the impact of dietary antioxidant supplementation during chemotherapy on both side effect and treatment efficacy outcomes. We will use a scoping review approach to identify what systematic review evidence exists regarding beneficial and harmful effects of dietary antioxidant supplements when used during cancer treatment.

Methods and analysis: We will use Arksey & O'Malley and Joanna Briggs Institute methods for scoping reviews. We will systematically search PubMed, Embase, CINAHL, Scopus, Dissertations & Theses Global, and the Cochrane Library from inception to October 2020. Systematic reviews of randomized controlled trials of oral dietary antioxidant supplements used by participants receiving curative chemotherapy, radiotherapy, or other biological therapy for cancer will be eligible. Two reviewers will screen citations and full texts for inclusion and chart data on research questions from included reviews. Two reviewers will assess the overall confidence in systematic review results using AMSTAR-2, and summarized evidence will focus on reviews rated at high or moderate overall confidence. Tables will be used to map existing evidence and identify evidence gaps for safety and effectiveness outcomes.

Ethics and dissemination: This scoping review does not require ethical approval as it is a secondary assessment of available literature. The results will be presented at conferences and submitted for publication in a peer-reviewed journal. We will also disseminate results to

community and clinical stakeholders and involve them in developing subsequent research to address critical existing gaps in the evidence as identified by the scoping review.

ARTICLE SUMMARY

Strengths and limitations of this study

- This will be the first scoping review to provide an up-to-date overview of the available systematic review literature on the potential benefits and harms of antioxidant dietary supplement use during curative treatment for cancer.
- The review will focus on understanding whether existing systematic reviews have examined the relationship between the use of antioxidant dietary supplements and the therapeutic efficacy of chemotherapy.
- The review will use the AMSTAR-2 tool to distinguish between systematic reviews providing different levels of certainty for results and emphasize reviews at overall high or moderate certainty.
- Results from this scoping review will be used to further the understanding of the breadth of antioxidant dietary supplement interventions and their effects during chemotherapy and to identify current gaps in knowledge.

INTRODUCTION

Cancer is the second leading cause of death in the United States,[1] having a significant deleterious impact on individual patients and society at large. Approximately 1 in 2 men and 1 in 3 women will develop cancer in their lifetime.[2] Cancer treatment is a broad area of research, as cancer is a complex, dynamic set of diseases, requiring newer technologies and innovative treatments with fewer adverse effects. Conventional medical therapies for those with cancer include but are not limited to chemotherapy and radiotherapy, both of which are associated with potentially debilitating side effects and reduced quality of life.[3]

Chemotherapy is a treatment approach designed to stop cancer growth either by preventing the reproduction of new cancer cells or killing cancer cells directly. Most chemotherapy drugs target the cell cycle, by altering or damaging deoxyribonucleic acid (DNA) in the cell.[4] One of the most significant causes of oxidative stress and inflammation is related to DNA damage.[5] Additionally, anti-cancer drugs cannot distinguish between cancer cells and healthy cells, which is thought to be a reason for chemotherapy's negative side effects.[4, 6] A majority of patients receiving chemotherapy report at least one side effect from the drug, most notably fatigue, nausea, vomiting, diarrhea, pain, rash, constipation, and shortness of breath.[6] For this reason, patients receiving cancer treatment often seek complementary and alternative adjuvant therapies to reduce side effects and improve quality of life.

A popular group of complementary therapies used by cancer patients is antioxidants, which can be administered through dietary interventions, intravenous infusion, or most commonly, dietary supplementation.[7] Antioxidants are substances that act to prevent or delay cellular damage, notably by stabilizing free radicals and reducing oxidative stress. The observation in laboratory studies that antioxidants decrease oxidative stress has made the use of antioxidants

common, albeit somewhat controversial, in the attempt to prevent or treat chronic disease.[8] Commonly used antioxidants include vitamins, minerals, phytochemicals and other related substances, and amino acids.[9]

While antioxidant supplements are popular among the general public, the evidence on antioxidant supplementation to prevent chronic disease or improve health outcomes is equivocal.[10-12] Although there is an increased willingness of medical professionals to use complementary therapies, the belief persists among many providers that alternative therapies could harm patients.[13-15] When patients use over the counter (OTC)dietary supplements without informing their physician, this may increase risk of interactions with prescription medications and undermine the patient-provider relationship.[16, 17]

A 2016 overview concluded that antioxidant supplementation reduces adverse effects and chemotoxicities from chemotherapy, though the authors noted inconsistencies in the literature.[9] The most studied oral antioxidant supplement may be melatonin, shown in vitro to have anti-tumor activity when used with irradiation.[18] However, while some research suggests that oral antioxidant supplementation during chemotherapy may increase patient survival, other research suggests that it may diminish the efficacy of the chemotherapeutic treatment.[19, 20] There is concern that antioxidant therapies may interact with the cytotoxic effects of chemotherapy, lessening adverse side effects and improving quality of life, but also rendering the cancer treatment less effective.[21] For example, a recently published secondary data analysis from a clinical trial comparing chemotherapy schedules in breast cancer identified an increased hazard of recurrence in women using antioxidant supplements both before and during chemotherapy.[22]

We are aware of many studies over the past twenty years that discuss dietary supplements during cancer treatment; several of these are systematic reviews.[9, 23-29] However, most

systematic reviews focus on the potential reduction in chemotherapy side effects with supplements. We are not aware of a review systematically collecting evidence on the relationship between antioxidant supplements and therapeutic response to chemotherapy, with the exception of one systematic review conducted more than 10 years ago.[30] Since publication of that review, there have been changes in chemotherapy regimens and antioxidant use patterns, and more current systematic reviews may have captured but not highlighted relevant information on response to chemotherapy. There is, therefore, a need to systematically identify the best currently available evidence on this topic. Currently, there is no comprehensive overview of the literature outlining the benefits and harms of antioxidant supplements for patients receiving conventional cancer therapies, and evidence appears particularly scant on the question of whether antioxidant supplementation may negatively interact or interfere with chemotherapeutic treatment. This apparent paucity of evidence precludes the ability to make evidence-based recommendations on use of antioxidant supplements by cancer patients.

Although we have not identified recent systematic reviews on the topic of antioxidant supplementation and effectiveness of cancer therapies, we think it is possible that for some antioxidants the question of a relationship between supplementation and efficacy of treatment may have already been asked and possibly even answered by systematic reviews of randomized controlled trials, perhaps as one component of reviews on the effects of antioxidant supplements on treatment side effects. We do not wish to undertake a large systematic review on the topic if some areas have already been addressed, and it is unclear if the area is ready for an overview of systematic review findings, given that the topic itself may be underexplored. Our goal is to evaluate the status of systematic review research questions on antioxidant oral supplementation during cancer treatment, with a particular focus on whether and how antioxidant effects upon

chemotherapy have been addressed. This information will provide direction, in conjunction with guidance from patient and clinician stakeholders, on the next steps in addressing this critical topic.

We will use scoping review methodology to identify and compile the data from previous systematic reviews of randomized controlled trials (RCTs) regarding not only the reduction of chemotherapy side-effects but also the efficacy of chemotherapy when oral antioxidant supplements are used in conjunction by persons with cancer. A scoping review is a form of knowledge synthesis that 'aims to map key concepts, types of evidence, and gaps in a defined area or field by systematically searching, selecting, and charting available evidence.'[31] Extracting information from systematic reviews will allow us to identify what is known and where there remain knowledge gaps on the topic. Specifically, this paper is focused on identifying 1) to what extent previous systematic reviews of RCTs have assessed the efficacy of chemotherapy in the presence of adjuvant antioxidant supplementation, and 2) what is known from systematic reviews of RCTs on the potential benefits and harms of adjuvant antioxidant supplementation during chemotherapy for cancer, including relationships between supplementation and the efficacy of chemotherapy. The results will inform future cancer research activities in this area.

METHODS

This protocol follows the Joanna Briggs Institute (JBI) guidance on protocols for scoping reviews and has been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist.[32, 33] The completed scoping review will be reported in accordance with the PRISMA extension for scoping reviews (PRISMA-ScR).[32]

We will follow the Arksey and O'Malley scoping review framework, modified by Levac 2010 and JBI (2017 and 2020),[34-38] consisting of the following steps:

(1) Identifying the research question;

(2) Identifying relevant studies;

(3) Selecting studies for inclusion;

(4) Charting data from included studies;

(5) Collating, summarizing and reporting the results;

(6) Consultation (optional, included).

Step 1: Identifying the research question

The areas of uncertainty concerning the use of antioxidant supplements during chemotherapy for cancer have been described above. We will answer the following research questions:

1) Among systematic reviews of RCTs on antioxidant supplements during chemotherapy, to what extent have research questions been posed regarding the effects of antioxidant supplementation on the therapeutic efficacy of chemotherapy?
2) What systematic review evidence exists regarding the use of antioxidant dietary supplements during chemotherapy with respect to:

   a) whether supplementation with specific antioxidants promotes or attenuates the efficacy of chemotherapeutic treatment?

   b) improvement of chemotherapy-related side effects and quality of life? and

   c) adverse clinical effects potentially associated with antioxidant supplementation?

Step 2: Identifying relevant studies

Types of evidence sources

The types of evidence of interest for this scoping review will be systematic reviews of RCTs. This is the most efficient way to identify comprehensive evaluations of available high-quality evidence. For the purposes of this scoping review, we will define systematic reviews of

RCTs as reviews that: 1) have a clear research question; 2) specify eligibility criteria for including studies; 3) seek to comprehensively identify RCTs relevant to the research question; 4) report the critical appraisal (e.g., risk of bias) of the included RCTs; and 5) present a synthesis, either quantitative or qualitative, of the characteristics and findings of the RCTs.[39] We will include systematic reviews focused on efficacy, effectiveness, or safety. We will include both published and unpublished systematic reviews but will exclude those reported solely as conference abstracts because they generally contain limited information. We will not exclude systematic reviews on the basis of language or date of publication.

While the current approach focuses on evidence from systematic reviews of RCTs, we will not exclude reviews that also seek to identify additional sources of evidence (e.g., observational studies). Furthermore, narrative (non-systematic) reviews addressing our outcomes of interest will be excluded initially but may be given secondary consideration dependent upon the quantity of systematic reviews identified. Depending on when the last search was run for the systematic reviews we identify and if time permits, we may also search for RCTs published since that date to ensure we have captured the most recently published evidence. While we believe that scoping systematic reviews of RCTs is the most practical first step in characterizing the body of evidence on this topic, the flexibility of the scoping approach permits us to extend our investigation beyond systematic reviews, if the results of our initial scoping suggests that this could be useful, and time and resources permit.

Data sources and search for studies

The initial search strategy was developed by an experienced medical information specialist (EFG) in collaboration with the remainder of the review team. The search strategy will be finalized after peer-review by another experienced medical information specialist using the PRESS Peer

Review of Electronic Search Strategies.[40] Databases searched from inception will include PubMed (Pubmed.gov), Embase (Embase.com), CINAHL (EBSCOhost), Scopus (Scopus.com), Dissertations & Theses Global (ProQuest), and the Cochrane Library (WileyOnline). A combination of keywords and subject headings will be adapted for use according to the specifications of each database. All records retrieved will include at least one antioxidant-related term and a term related to cancer therapies. Examples of antioxidant terms include but are not limited to vitamin C, lycopene, and melatonin. Cancer therapy terms include but are not limited to chemotherapy, radiotherapy, antineoplastic, and anticancer. The initial search strategy for Embase, which resulted in retrieval of more than 7000 records, is reported in Appendix 1. In addition to screening records retrieved from searching bibliographic databases, we will search the PROSPERO database of registered systematic reviews, scan the reference lists of included reviews and contact experts in the field to identify additional relevant systematic reviews.

Step 3: Selecting studies for inclusion

We will use the PCC (Population, Concepts and Context) framework to implement eligibility criteria for included studies.[38]

Population

Participants with cancer who are receiving chemotherapy, radiotherapy, or other biological therapy for treatment of cancer will be sought. There will be no restrictions by population characteristics (e.g., sex, age, comorbidities, geographic location), or type or stage of cancer.

Concepts

The core intervention of interest is antioxidant dietary supplements concomitant with chemotherapy, radiotherapy, or other biological therapy for cancer. We are defining antioxidant dietary supplements as orally-consumed products with known ability to prevent cellular damage

by reacting with oxidizing free radicals.[41] Antioxidant dietary supplements cover a wide range of substances, including vitamins (e.g. vitamin C), minerals (e.g. selenium), amino acids (e.g. n-acetylcysteine), carotenoids (e.g. lycopene), botanicals (e.g. polyphenols), and hormones (e.g. melatonin). Studies involving IV administration of antioxidants in a medical setting (e.g., IV vitamin C) will be excluded from this scoping review. Oral and IV antioxidants are not only processed differently by the body but oral supplements may be taken by patients without direct assistance of medical professionals, and thus have different clinical and public health implications. Studies involving mushrooms and mushroom products will be excluded because their mechanism is primarily through immunomodulation.[42] Studies involving compound herbal formulas will also be excluded due to the potential for multiple mechanisms of activity that confound the research question. Finally, although many foods such as fruits and vegetables are good sources of antioxidants, whole food dietary interventions (e.g., changes in food habits) will also be excluded from this scoping review due to the potential for confounding by non-antioxidant dietary components with known activity against cancer (e.g., histone deacetylase (HDAC)-inhibition, DNA methylation).[43, 44]

The core outcomes of interest will consist of 1) therapeutic response to treatment with chemotherapy, radiotherapy, or other biological therapy, 2) improvements in chemotherapy-related side effects and quality of life, and 3) increases in adverse effects potentially related to antioxidant supplementation. Response to treatment may be measured as mortality or with indicators of morbidity (e.g., cancer progression, recurrence). Because it may not be possible to establish whether side effects and other adverse events are more likely related to the cancer treatment or to the supplement use, we will document when adverse events are presented within

the reviews as side effects due to either cancer treatment or supplement use, but we will discuss the findings both separately and jointly. We will include outcomes measured at any time point.

Context

The context is cancer treatment with curative intent. The palliative use of chemotherapy, radiotherapy, or other biological therapies will be excluded because a core aspect of this scoping review is the evaluation of the evidence on antioxidant supplements with regard to possible interference with the curative objectives of treatment. We will not restrict context by date, healthcare setting or country.

Data management

Citations for retrieved records will be downloaded into EndNote X8 and deduplicated. Citations will then be uploaded to Covidence and screened for inclusion in two stages.[45] At the first stage, two team members will independently screen all records for relevance on the basis of record title and abstract. Prior to title and abstract screening, the team members will carry out a pilot screening of randomly selected records, to ensure that they understand and agree upon the initial inclusion criteria. During the title and abstract screening, discrepancies between screeners will regularly be resolved, to prevent development and continuation of differing interpretations of the inclusion criteria.[46] All records that are deemed to be potentially relevant to the scoping review will progress to full text screening. Once records are ready for full text screening, a calibration exercise will be performed in which all team members screen a set of the same randomly selected 25 records against the inclusion and exclusion criteria for the review. The results of this screening will be compared between team members, and any necessary clarifications to the inclusion and exclusion criteria, or modifications of those criteria, will be made and documented in the completed scoping review. After any clarification or modification of the selection criteria,

and agreement among the team on the results of the calibration exercise, two team members will independently screen each full text record for inclusion. Discrepancies between screeners will be resolved by discussion or involvement of a third team member. The study citation and brief reason for exclusion will be provided for each excluded record and a flow chart of the screening process will be provided in accordance with PRISMA-ScR.

Step 4: Charting data from included studies

Data will be extracted from each included systematic review. These data will include bibliographic information (e.g., authors, date of publication, journal of publication), information on the methods (e.g. the research question, study enrollment criteria and design), information on results, and the key findings for each included review. See Appendix 2 for a draft of the data charting form displaying the elements to be extracted from each review. To ensure that the data charting form is comprehensive and clear, we will pilot test the form prior to embarking on the full data extraction. Three members of the author team will use the form to chart data from the same three reviews and compare the extracted information across authors. Anything that is unclear or missing from the data charting form will be discussed and clarifications and modifications will be addressed in collaboration with the full author team until all authors are satisfied that the data charting form is suitable for extraction of all relevant results. Data extraction will then be carried out for each study by one author and verified by a second author.

Quality Assessment

Although critical assessment of the evidence is optional for scoping reviews, previous research has estimated that almost one-quarter of scoping reviews do include a critical appraisal step.[47] Methodological shortcomings in the conduct of systematic reviews may lead to incomplete and biased findings and reduce our confidence in review conclusions. Because we wish

to concentrate on available systematic review evidence in which we can have confidence, we will carry out a critical assessment of the systematic reviews we find.

In addition to extracting key data from all systematic reviews, we will carry out and report an assessment of the conduct of each of the included systematic reviews, using the updated version of AMSTAR (A Measurement Tool to Assess Systematic Reviews) (AMSTAR-2).[48] AMSTAR-2 is a critical appraisal tool for systematic review conduct that is based upon 16 yes/no questions about the conduct of the review. Four of these questions are considered to be of critical importance. Based upon the total number of apparent flaws in review conduct, and whether any of these flaws are of critical importance, the overall confidence in the results of the systematic review is rated at one of four levels: high, moderate, low, and critically low. The interpretation of an overall high level of confidence is that "the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest," while the interpretation of an overall low level of confidence is that "the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest."[48] See Appendix 3 for the detailed AMSTAR-2 rating criteria, rubric, and interpretation for overall assessment of confidence in review results. AMSTAR-2 assessment will be carried out for each study by one author and verified by a second author.

We will highlight the charted data extracted from the reviews judged at moderate or high level of confidence, and we may also extract additional data, using the methods described above to develop and pilot an additional data charting form, to capture further details on the findings of these reviews.

Step 5: Collating, summarizing and reporting the results

As scoping reviews do not formally synthesize the evidence, this review will provide a descriptive summary of the evidence and map this summary against the objectives of the review. For example, we will identify evidence on individual antioxidants with regard to the questions of interest from each review, indicating the underlying populations (types and stages of cancer, chemotherapeutic regimens) the evidence is sourced from, and the AMSTAR-2 rating of the reviews providing this information. Results will be presented in tables and charts, with frequencies calculated for data elements when appropriate (e.g., the number of reviews on a particular antioxidant). We will conclude by discussing whether we believe there is reliable systematic review evidence on the potential benefits and risks of antioxidant supplements during chemotherapy and suggesting potential avenues for further research.

Step 6: Consultation

As described under the Data sources and search for studies, we will consult experts in the field to identify additional systematic reviews not found through database searching. We will also consult with stakeholders in cancer treatment (e.g., clinicians, patients) to inform the elements to be included in the data charting. Through consultation with these stakeholders we will ensure that relevant characteristics of the populations, interventions, and outcomes are captured and important gaps in the evidence may be identified. In keeping with best practices in community-engaged research, we will disseminate the findings of the review to community stakeholders and patients. Community engagement will also be used to inform recommendations for future research based on the review.

Ethics and dissemination

This scoping review does not require ethics approval as it is a secondary review of the literature. Based upon the results of this review, we will disseminate our findings of both reliable

evidence (where it exists) or a gap in reliable evidence and a need for additional research. This dissemination will be carried out through presentations at relevant conferences and publication in a peer-reviewed open-access journal. As mentioned above, we will also disseminate the findings to community and patient stakeholders. We will ask these stakeholders to join with clinical and research stakeholders to identify the best ways to address any critical existing gaps in the evidence (e.g., a focused systematic review, further randomized trials) and prioritize the next steps.

Patient and public involvement

As described above, we will consult with patients to inform the development of data charting. We will also engage with patients, clinicians and other stakeholders to disseminate summaries of the review findings in appropriate formats and venues. Finally, we will involve patients and the public in developing and prioritizing future research activities based upon the findings of this project.

DISCUSSION

The impact of oral antioxidant supplementation upon the effectiveness of curative therapies for cancer is of critical importance for patients who use these supplements to reduce treatment side effects and improve quality of life. Because oral antioxidant supplements are used to mitigate the side effects of cancer therapies, it is expected that antioxidant supplementation will lead to better tolerance for therapy, and thus to improved outcomes for patients. However, if antioxidant supplements interfere with the cytotoxic effects of chemotherapy, the cancer treatment may become less effective and lead to worse rather than better patient outcomes. Recent observational data has suggested that antioxidant supplements during and after cancer treatment are associated with an increased risk of cancer recurrence, raising concern about the place of antioxidant supplements during treatment for cancer.[22]

Because we are unsure to what extent the relationship between antioxidant supplements and the effectiveness of cancer therapies has been assessed in the research literature, we are conducting a scoping review to explore this. We are focusing our exploration on systematic reviews of randomized trials because they are summaries of the highest level of evidence on the effects of interventions. We believe that most systematic reviews in this area have focused on the effectiveness of supplements in ameliorating side effects and improving quality of life, but that these reviews may incorporate research questions on the effectiveness of chemotherapy in the presence of antioxidant supplementation. Identifying where these research questions have been asked, and with what results, will be a first step in identifying gaps in the evidence base and developing a plan of research to ensure that the relationship between antioxidant supplements and the effectiveness of cancer therapies is understood.

Implications

We will use the findings from this review to develop to develop future research priorities and initiatives to help fill remaining critical gaps in the current literature and contribute to key next steps. We will then work with patients and clinicians to prioritize evidence needs, and consult with clinical, research, and patient stakeholders on the most appropriate methods (e.g., new or updated systematic reviews versus additional primary studies) for addressing these gaps. Near the end of the scoping review process, when we are able to characterize the extent of available reliable evidence, we will begin to formalize partners and processes for these next steps. Our target date for completion of this scoping review is the second half of 2021.

Potential limitations and mitigation strategies

Though scoping the entirety of observational and clinical evidence on this topic is beyond the scope of the current initiative, we believe that focusing on systematic reviews is the most

efficient first step in characterizing the weight of the current research evidence. We are also uncertain about the volume of review evidence, which makes it difficult to plan ahead for either superficial or very detailed data extraction. The iterative nature of scoping reviews allows us to be flexible in response to the quantity and quality of the evidence and prioritize summarizing evidence according to characteristics such as review quality or recency. Regular engagement with clinical and research partners during the conduct of the scoping review will allow us to modify our methods in such a way as to develop summaries of review evidence that are maximally relevant and useful to inform practice. We plan to ensure the transparency of our methods by devoting a section of the final publication to changes from and refinements to this protocol, together with the rationale for any revisions. At the conclusion of this project we will develop a plan, including potential future funding applications, for the next steps in a research agenda to inform decisions by patients and providers on the potential benefits or harms of dietary antioxidant supplementation during chemotherapy.

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Author Contributions: AE, CLK, and CD jointly conceived the study and developed the research questions. LSW proposed the scoping review methodology and developed the protocol with IM and SS. EFG developed the search strategy. LSW drafted the manuscript. All authors revised the manuscript and approved the final text. LSW is guarantor of the review.

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47. Pham MT, Rajic A, Greig JD, et al. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. *Res Synth Methods* 2014;5(4):371-85.
48. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017:j4008-j.

APPENDIX 1 – EMBASE PRELIMINARY SEARCH STRATEGY

Embase (Embase.com) – 7253 references retrieved on 06 October 2020

One-line search run in Results tab of Embase.com platform:

('antioxidant'/exp OR antioxidant*:ti,ab,kw OR 'anti-oxidant*':ti,ab,kw OR antioxidat*:ti,ab,kw OR 'anti-oxidat*':ti,ab,kw OR 'antioxidant activity'/exp OR 'acetylcysteine'/exp OR acetylcystein*:ti,ab,kw OR 'acetyl cysteine':ti,ab,kw OR acetadote:ti,ab,kw OR mucomyst:ti,ab,kw OR cetylev:ti,ab,kw OR 'arginine'/exp OR arginin*:ti,ab,kw OR 'ascorbic acid'/exp OR 'ascorbic acid*':ti,ab,kw OR 'vitamin c':ti,ab,kw OR ascorbate:ti,ab,kw OR 'ascorbyl palmitate':ti,ab,kw OR 'carotenoid'/exp OR caroten*:ti,ab,kw OR 'coumarin'/exp OR coumarin*:ti,ab,kw OR cumarin*:ti,ab,kw OR 'curcumin'/exp OR curcumin*:ti,ab,kw OR turmeric:ti,ab,kw OR 'ellagic acid'/exp OR 'ellagic acid*':ti,ab,kw OR 'benzoanic acid*':ti,ab,kw OR 'benzoaric acid*':ti,ab,kw OR 'melatonin'/exp OR melatonin*:ti,ab,kw OR circadin:ti,ab,kw OR 'polyphenol'/exp OR polyphenol*:ti,ab,kw OR 'retinol'/exp OR retinol:ti,ab,kw OR 'vitamin a':ti,ab,kw OR 'retinyl palmitate':ti,ab,kw OR 'retinoic acid*':ti,ab,kw OR 'selenium'/exp OR selenium:ti,ab,kw OR selenicum:ti,ab,kw OR 'tocopherol'/exp OR tocopherol*:ti,ab,kw OR tocoferol:ti,ab,kw OR 'vitamin e':ti,ab,kw OR 'ubiquinone'/exp OR ubiquinone:ti,ab,kw OR 'vitamin q':ti,ab,kw OR 'coenzyme q10':ti,ab,kw OR coq10:ti,ab,kw OR 'coenzyme q':ti,ab,kw OR 'zinc'/exp OR zinc:ti,ab,kw OR zincum:ti,ab,kw OR 'thioctic acid'/exp OR 'thioctic acid*':ti,ab,kw OR 'lipoic acid*':ti,ab,kw OR 'resveratrol'/exp OR resveratrol:ti,ab,kw OR 'glutathione'/exp OR glutathione:ti,ab,kw OR glutathiol:ti,ab,kw OR 'chlorogenic acid'/exp OR 'chlorogenic acid*':ti,ab,kw OR 'ferulic acid'/exp OR 'ferulic acid*':ti,ab,kw OR 'ferulate sodium':ti,ab,kw OR 'sodium ferulate':ti,ab,kw OR 'lycopene'/exp OR lycopene:ti,ab,kw OR

'docosahexaenoic acid'/exp OR docosahexaeno*:ti,ab,kw OR 'icosapentaenoic acid'/exp OR 'icosapentaenoic acid*':ti,ab,kw OR 'eicosapentaenoic acid*':ti,ab,kw OR 'vitamin supplementation'/exp OR 'vitamin supplement*':ti,ab,kw OR 'hibiscus'/exp OR hibiscus:ti,ab,kw OR 'folic acid'/exp OR 'folic acid*':ti,ab,kw OR folate:ti,ab,kw OR 'catechin'/exp OR catechin*:ti,ab,kw OR 'catechuic acid*':ti,ab,kw OR ciandiol:ti,ab,kw OR 'anthocyanidin'/exp OR anthocyanidin:ti,ab,kw OR 'tannin'/exp OR tannin*:ti,ab,kw OR 'tannic acid*':ti,ab,kw OR gallotanni*:ti,ab,kw OR 'rutoside'/exp OR rutoside:ti,ab,kw OR rutin:ti,ab,kw OR rutinoside:ti,ab,kw OR 'vitamin p':ti,ab,kw OR 'isoflavone'/exp OR isoflavone*:ti,ab,kw OR 'quercetin'/exp OR quercetin*:ti,ab,kw OR quercitin*:ti,ab,kw OR quercetol*:ti,ab,kw OR 'lignan'/exp OR lignan*:ti,ab,kw OR 'allicin'/exp OR allicin:ti,ab,kw OR '5 methoxytryptamine'/exp OR methoxytryptamine:ti,ab,kw OR mexamine:ti,ab,kw OR 'uric acid'/exp OR 'uric acid*':ti,ab,kw OR 'urobilinogen'/exp OR urobilinogen:ti,ab,kw OR urinobilinogen:ti,ab,kw OR 'melanoidin'/exp OR melanoidin:ti,ab,kw OR 'phytic acid'/exp OR 'phytic acid*':ti,ab,kw OR 'phytinic acid*':ti,ab,kw OR 'saponin'/exp OR saponin*:ti,ab,kw OR glycosaponin*:ti,ab,kw OR 'methionine'/exp OR methionin*:ti,ab,kw OR levomethionine:ti,ab,kw OR methiolate:ti,ab,kw OR 'albumin'/exp OR albumin:ti,ab,kw OR albumen:ti,ab,kw OR 'lactoferrin'/exp OR lactoferrin*:ti,ab,kw OR lactotransferrin*:ti,ab,kw OR 'chromium'/exp OR chromium:ti,ab,kw OR 'transferrin'/exp OR transferrin*:ti,ab,kw OR siderophilin:ti,ab,kw OR 'ferritin'/exp OR ferritin*:ti,ab,kw OR immunoferritin:ti,ab,kw OR 'manganese'/exp OR manganese:ti,ab,kw OR cutaval:ti,ab,kw OR 'molybdenum'/exp OR molybden*:ti,ab,kw OR 'fish oil'/exp OR 'fish oil*':ti,ab,kw OR promega:ti,ab,kw OR 'omega 3 fatty acid'/exp OR 'omega 3 fatty acid*':ti,ab,kw OR 'omega 3 carboxylic acid*':ti,ab,kw OR 'alternative medicine'/de OR 'alternative medicine*':ti,ab,kw OR 'complementary

medicine*':ti,ab,kw OR 'complementary therap*':ti,ab,kw OR 'diet supplementation'/exp OR 'diet* supplement*':ti,ab,kw) AND ('chemotherapy'/exp OR chemotherap*:ti,ab,kw OR 'radiotherapy'/exp OR radiotherap*:ti,ab,kw OR 'cancer therapy'/exp OR (((cancer OR radiation OR irradiation OR tumor* OR tumour* OR neoplas* OR oncolog*) NEAR/3 (therap* OR treat* OR inhibit*)):ti,ab,kw) OR 'adjuvant radiotherapy'/exp OR 'antineoplastic agent'/exp OR anticancer*:ti,ab,kw OR 'anti-cancer*':ti,ab,kw OR anticarcinogen*:ti,ab,kw OR 'anti-carcinogen*':ti,ab,kw OR 'antineoplastic activity'/exp OR antineoplastic*:ti,ab,kw OR 'anti-neoplastic*':ti,ab,kw OR antitumor:ti,ab,kw OR 'anti-tumor':ti,ab,kw OR antitumour:ti,ab,kw OR 'anti-tumour':ti,ab,kw OR 'chemoradiotherapy'/exp OR chemoradiotherap*:ti,ab,kw OR 'alkylating agent*':ti,ab,kw OR alkylator*:ti,ab,kw OR 'antimetabolite'/exp OR antimetaboli*:ti,ab,kw OR ‘anti-metaboli*’:ti,ab,kw OR 'antimitotic agent'/exp OR antimitotic*:ti,ab,kw OR 'anti-mitotic*':ti,ab,kw OR 'mitotic inhibitor*':ti,ab,kw OR 'mitosis inhibitor*':ti,ab,kw OR 'anthracycline'/exp OR anthracyclin*:ti,ab,kw OR 'protein tyrosine kinase inhibitor'/exp OR 'tyrosine kinase inhibitor*':ti,ab,kw OR tki:ti,ab,kw OR 'tyrosine protein kinase inhibitor*':ti,ab,kw OR 'protein serine threonine kinase inhibitor'/exp OR 'serine threonine kinase inhibitor*':ti,ab,kw OR 'checkpoint inhibitor'/exp OR 'checkpoint inhibitor*':ti,ab,kw OR 'anti pd1':ti,ab,kw OR 'anti pdl1':ti,ab,kw OR 'antimyeloma activity'/exp OR antimyeloma*:ti,ab,kw OR 'anti-myeloma*':ti,ab,kw OR 'dna topoisomerase inhibitor'/exp OR 'topoisomerase inhibitor*':ti,ab,kw OR 'topoisomerase 1 inhibitor*':ti,ab,kw OR 'topoisomerase i inhibitor*':ti,ab,kw OR 'antiandrogen'/exp OR 'antiandrogen therapy'/exp OR 'anti-androgen*':ti,ab,kw OR antiandrogen*:ti,ab,kw OR 'androgen antagonist*':ti,ab,kw OR 'antiestrogen'/exp OR 'anti-estrogen*':ti,ab,kw OR 'anti-oestrogen*':ti,ab,kw OR antiestrogen*:ti,ab,kw OR antioestrogen*:ti,ab,kw OR 'estrogen antagonist*':ti,ab,kw OR

'oestrogen antagonist*':ti,ab,kw OR 'cancer hormone therapy'/exp OR 'cancer hormone therap*':ti,ab,kw OR 'cancer patient'/exp OR 'cancer patient*':ti,ab,kw OR 'oncolog* patient*':ti,ab,kw OR electrochemotherap*:ti,ab,kw OR photochemotherap*:ti,ab,kw OR chemoembolization:ti,ab,kw OR chemoembolisation:ti,ab,kw OR carcinochemotherap*:ti,ab,kw OR multichemotherap*:ti,ab,kw OR polychemotherap*:ti,ab,kw OR antileukemi*:ti,ab,kw OR 'anti-leukemi*':ti,ab,kw OR antileukaemi*:ti,ab,kw OR 'anti-leukaemi*':ti,ab,kw OR antimetasta*:ti,ab,kw OR 'anti-metasta*':ti,ab,kw OR antimutagen*:ti,ab,kw OR 'anti-mutagen*':ti,ab,kw) AND (metaanaly*:ti,ab,kw OR 'met analy*':ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR (((systematic* OR methodologic* OR collaborative OR integrative) NEAR/3 (review* OR overview*)):ti,ab,kw) OR ((pool* NEAR/3 analy*):ti,ab,kw) OR handsearch*:ti,ab,kw OR 'hand search*':ti,ab,kw OR 'data synthes*':ti,ab,kw OR 'data extraction*':ti,ab,kw OR 'data abstraction*':ti,ab,kw OR metaregression*:ti,ab,kw OR 'meta regression*':ti,ab,kw OR [cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

APPENDIX 2 – DRAFT ELEMENTS FOR DATA CHARTING

Bibliographic characteristics

Journal name
Year of publication
Country of corresponding author
Funding

Review question and methods

Review protocol cited/provided
Inclusion criteria for participants: types of cancer(s), stage, other disease characteristics
Inclusion criteria for participants: age, sex, other demographic characteristics
Inclusion criteria for participants: cancer treatment(s)
Inclusion criteria for interventions: specific supplements or categories of supplements
Inclusion criteria for comparators:
Outcomes sought from included studies (including not only domain but also instrument or scale and time frame if specified): [may break down by type eg, quality of life, adverse effect, success of cancer treatment]
Study designs eligible for inclusion:
List of databases searched
Total number of databases searched
Date of last database search
Quality assessment tool
Planned meta-analyses, subgroup analyses and sensitivity analyses

Planned methods to assess the quality/certainty of effect estimate

Review results and analyses from included* RCTs

Number of included RCTs
Number of participants in included RCTs
Age, sex, other demographic characteristics of participants in included RCTs
Cancer characteristics of participants in included RCTs
Cancer treatment(s) provided to participants in included RCTs
Antioxidant interventions in included RCTs
Comparators in included RCTs:
Outcomes present in included RCTs:
List of meta-analyses conducted
List of subgroup analyses conducted
List of sensitivity analyses conducted

*all references to included studies refer to those studies assessing effects of oral antioxidant supplement interventions during curative treatment for cancer; systematic reviews may have a broader scope.

For each review, results for each antioxidant-related PICO question

Participant/Intervention/Comparator/Outcome/Time (may group multiple time points)
Are any results presented?
If so, were results qualitative or quantitative?
If quantitative, what was the effect estimate?
Quote or summary of author assessment of findings on the PICO question

Certainty/quality of evidence for the results (if assessed by authors)
Confidence in results of the review (see AMSTAR 2 assessment)

APPENDIX 3 – AMSTAR-2 CRITERIA FOR CONFIDENCE IN THE RESULTS OF SYSTEMATIC REVIEWS

AMSTAR-2 criteria [47]
1. Did the research questions and inclusion criteria for the review include the components of PICO? (Y, N)
2. Did the report of the review contain explicit statement that the review methods were established prior to conduct of the review? (Y, PY, N)
3. Did the review authors explain their selection of the study designs for inclusion in the review? (Y, N)
4. Did the reviewer authors use a comprehensive literature search strategy? (Y, PY, N) CRITICAL FLAW if not Y, PY
5. Did the review authors perform study selection in duplicate? (Y, N)
6. Did the review authors perform data extraction in duplicate? (Y, N)
7. Did the review authors provide a list of excluded studies and justify the exclusions? (Y, PY, N)
8. Did the review authors describe the included studies in adequate detail? (Y, PY, N)
9A. RCTS- Did authors use a satisfactory technique for assessing the risk of bias (ROB) in individual studies that were included in the review? (Y, PY, N, NA- includes only NRSI) CRITICAL FLAW if not Y, PY
9B. NRSI- Did authors use a satisfactory technique for assessing the risk of bias (ROB) in individual studies that were included in the review? (Y, PY, N, NA- includes only RCTs) CRITICAL FLAW if not Y, PY

10. Did the review authors report on the sources of funding for the included studies? (Y, N)
11A. RCTs- If meta-analysis was performed did the authors use appropriate methods for statistical combination of results? (Y,N, only NRSI, No MA) CRITICAL FLAW if not Y, PY
11B. NRSI- If meta-analysis was performed did the authors use appropriate methods for statistical combination of results? (Y,N, only RCTs, no MA) CRITICAL FLAW if not Y, PY
12. If meta-analysis was performed, did the review authors assess the potential impact of ROB in individual studies on the results of the meta-analysis or other evidence synthesis? (Y, N, No MA, No QA)
13. Did the review authors account for ROB in individual studies when interpreting/discussing the results of the review? (Y, N, No QA) CRITICAL FLAW if not Y, PY
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (Y, N)
15. Did the review authors carry out an adequate investigation of publication bias, and discuss its likely impact on the results of the review? (Y, N)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for the review? (Y, N)
Number of critical flaws (critical items answered N):
Number of non-critical flaws (non-critical items answered N):
Rubric for overall confidence: High confidence: no critical flaws with zero or one non-critical flaw.

Moderate confidence: no critical flaws with > 1 non-critical flaw. Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence Low confidence: one critical flaw with or without any non-critical flaws Critically low confidence: more than one 1 critical flaw with or without any non-critical flaws.
Overall confidence in the results of the review (High/Moderate/Low/Critically Low):
Interpretation of quality levels: High: The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. Moderate: The systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review Low: The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest Critically Low: The review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	pg 1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A not an update
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A not registered as PROSPERO does not register scoping reviews
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	pg 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	pg. 18

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A not an amendment
Support			
Sources	#5a	Indicate sources of financial or other support for the review	pg. 18
Sponsor	#5b	Provide name for the review funder and / or sponsor	pg. 18
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	pg. 18
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	pg 5-8
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	pg 7-9
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	pg 9-12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	pg 10
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	pg 12

Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	pg 12-13
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	pg 13
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	pg 13-14, Appendix 2
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	pg 13-14, Appendix 2
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	pg 14, Appendix 3
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	N/A no quantitative synthesis planned
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	N/A no quantitative synthesis planned
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A no quantitative synthesis planned
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	pg 15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A no quantitative synthesis planned
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A individual reviews to be scoped but body of

evidence evidence not assessed for confidence

Notes:

- 1b: N/A not an update
- 2: N/A not registered as PROSPERO does not register scoping reviews
- 4: N/A not an amendment
- 12: pg 13-14, Appendix 2
- 13: pg 13-14, Appendix 2
- 14: pg 14, Appendix 3
- 15a: N/A no quantitative synthesis planned
- 15b: N/A no quantitative synthesis planned
- 15c: N/A no quantitative synthesis planned
- 16: N/A no quantitative synthesis planned
- 17: N/A individual reviews to be scoped but body of evidence not assessed for confidence This checklist was completed on 19. November 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai