Feature Article

Are Supra-Physiological Plant-Based Antioxidants Ready for the Clinic? A Scoping Review of Hormetic Influences Driving Positive Clinical Outcomes

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Abstract

Background: A pro-inflammatory metabolic state is key to the chronic disease epidemic. Clinicians' ability to use nutrients to balance inflammation via oxidant homeostasis depends on the quality of antioxidants research. Understanding the intersection of two prominent theories for how antioxidants quell inflammation—nutritional hormesis and oxidant scavenging—will enable therapeutic antioxidant use in clinical practice.

Purpose: We sought to survey the literature to answer the question: has the hormetic response of exogenous antioxidants been studied in humans and if so, what is its effect

Research Design: This review investigates the less well-established theory, nutritional hormesis. To understand the state of hormetic response research, we conducted a literature review describing the relationship between exogenous antioxidants, hormesis, and chronic disease. We used an adaptive search strategy (PubMed and Scopus), retrieving 343 articles, of which 218 were unique. Most studies reviewed the hormetic response in plant and cell models (73.6%) while only 2.2% were in humans.

Results: Given the limited robust evidence, clinicians lack research-based guidance on the appropriate therapeutic dose of exogenous antioxidants or, more concerning, supra-physiological dosing via supplements. A critical hurdle in searching the literature is the lack of standardized nomenclature describing the hormetic effect, challenging the ability of clinicians to make informed decisions.

Conclusion: Non-human research shows a biphasic, hormetic relationship with antioxidants but observational studies have yet to translate this into the complexities of human biochemistry and physiology. Therefore, we cannot accurately translate this into clinical care. To remedy this insufficiency, we suggest: (1) Improved data collection quality: controlled diet, standardized antioxidant measurements, bioavailability assessed via biomarkers; (2) Larger, harmonized datasets: research subject transparency, keyword standardization, consensus on a hormesis definition.

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Introduction

Inflammation and Chronic Disease

Inflammation—one result of a host's immune response to foreign proteins or cellular damage—is meant to be an acute physiologic process that is upregulated as part of immune activity and downregulated when threats are neutralized.[1] However, when the immune system sustains a chronic inflammatory state, it can cause damage at the cellular level by a mechanism called oxidative stress, which leads to tissue dysfunction and, over time, chronic disease.[2] Over 50% of Americans suffer from 1 or more chronic diseases that is either caused or prolonged by unresolved inflammation,[3] driven at the cellular level by oxidative stress. This stress creates a pro-oxidant state that reflects a disruption in homeostasis due to insufficient antioxidant availability to neutralize the unstable molecular oxidants that damage proteins, lipids, carbohydrates, and even DNA.[4,5] Despite this, inflammation is not simply a bad-actor but rather an imperative signal, which rallies innate and adaptive immune defenses against infection or tissue injury to instigate healing.[4,6] However, chronic, unresolved inflammation contributes to age-related diseases such as cognitive decline, atherosclerosis, arthritis, and sarcopenia, which are instigated by the damage caused from oxidative stress.[7-9] Thus, *the identification of therapeutic mechanisms to resolve oxidative stress and calm inflammation* is crucial to support prevention of chronic disease and promote healthy aging. In response to this challenge, the nutrition community turns to our most potent anti-inflammatory tools - whole foods and nutrients.

Clinical Use of Antioxidants

Clinicians are eagerly looking for specific guidance to support the use of antioxidants, whether through the diet or via supra-physiological doses as nutraceutical supplements, to achieve therapeutic outcomes and, most importantly, avoid harm. At present, there is no consensus regarding the risk-benefit calculus for the clinical use of some exogenous antioxidants–some studies report harm, while others report benefits.[10] On the other hand, there is substantial evidence showing that diets higher in minimally processed plant foods promote health and reduce disease.[11] The antioxidants present within these foods may mediate the positive effects; however, this remains uncertain. Although healthy dietary patterns have barriers to adoption, they are a crucial tool for fighting chronic inflammation and addressing chronic disease in patients. Nevertheless, much confusion exists around the clinical use of food (food as medicine) and the use of high doses of concentrated and refined nutrients in the form of nutraceuticals (supplementation) as anti-inflammatory agents. Almost 60% of Americans report supplement use; therefore, understanding the dose-response mechanism for specific antioxidants is necessary for precision in clinical practice.[12] This leads us to the very heart of our research question: **does a dose-response relationship exist with dietary antioxidants and our innate oxidant response system that would qualify as a hormetic response?**

Antioxidants are complex compounds that have multifactorial effects throughout the body. The categorization of plant-based antioxidants, a.k.a. phytochemicals or phytonutrients, is based on the molecular structure that gives rise to the varied functions these compounds serve. Over 8000 antioxidants are classified as phenols, with half coming from the flavonoid subclass.[13] Two polyphenols in particular, curcumin and resveratrol, are derived from foods, turmeric and red wine/grapes, that have shown strong correlations in observational studies with reduced risk of chronic disease and improved longevity.[14,15] The impact on human biochemistry of the isolation of these compounds from their health-promoting foods (removing them from the food matrix) is at the root of the research question of this review. If a phytochemical like curcumin is credited for antioxidant, anti-inflammatory, and anti-tumor activities, is there a point at which this highly concentrated compound whose health benefits were first recognized in a different format as part of a whole food, can create imbalance in the oxidative homeostasis and lead to negative outcomes? Do supra-physiologic doses of antioxidants through dietary supplements cause a hormetic response? Not to mention the potentially important entourage or food matrix effect that may be lost in the isolation process. In short, *are high doses of concentrated, isolated antioxidants harmful while low doses, as would mirror normal dietary intake, beneficial?*

Hormesis

Born in the science of toxicology, hormesis has historically been defined as the difference in effect of a chemical messenger when experienced at a low dose, which increases resiliency, vs that at a high dose, which induces toxicity.[16] The hormetic response to specific doses of stress is a foundational construct throughout the human body, as seen in the positive benefits from intermittent fasting,[17] physical exercise,[18] and mitochondrial replication or cognitive exercises among others,[19] which suggests its likely presence in other key functions like oxidant homeostasis. These hormetic

influences trigger biochemical processes that translate eustress into an activation of cellular defense signaling pathways that prove beneficial.[20] *But does this well-accepted phenomenon apply to dietary antioxidants as well?* A hormetic response means that this benefit is dose-dependent, too much of a stressor such as the restriction of eating at the heart of intermittent fasting will not have a beneficial but rather a detrimental impact. *Thus, if hormesis applies to exogenous antioxidants then it is imperative that we understand when this eustress becomes detrimental.*

Studies support the evolving theory that health benefits associated with high dietary intake of antioxidant-rich foods likely fight inflammation by triggering a protective cellular response either through reactive oxygen species (ROS) quenching (oxidant-scavenging) or through activation of key antioxidant pathways such as the NRF2-KEAP1 stress response network (hormetic response).[21] While the hormetic behavior of antioxidants is supported by the observation that the bioavailability of dietary polyphenols in the serum is very low while the subsequent polyphenol metabolites are more abundant,[22] the research community has not yet supported this hormetic theory with in vivo human trials. This observation raises important considerations regarding the role that the gastrointestinal tract (GIT) may play in selective uptake of nutrients as well as transforming antioxidants prior to absorption. Various elements influence the capacity of the GIT to digest and absorb antioxidants such as microbial species, epigenetic factors, anatomy, age, and many more. Therefore, interindividual variation in GIT adsorption is assured. Every person will likely have a different dietary intake threshold to exhibit a hormetic response. *A key consideration for the personalization of hormetic response in vivo is the important distinction between the dose of antioxidant given to an individual and the amount that becomes available to the individual's antioxidant response system known as the bioavailability.*

Aims and Scope

What is clear is that oxidant balance plays a critical role in the function of the human body and our ability to prevent and remedy chronic disease which is driven by unresolved inflammation. In this review, *we seek to outline the current state of research around the theory of nutritional hormesis and how that theory accommodates the multiple roles antioxidants play in human biochemistry.* In addition, we describe the challenges related to the translation of antioxidant research into clinical practice and provide our insights to bridge these barriers. We aim to support the field of antioxidant research to better guide clinical decisions by ensuring accurate translation of the epidemiological and laboratory-based findings of the last 10 years into the human patient population including harmonization of keywords.

Objectives

- Assess the strength of existing evidence for hormesis in humans from plant sources of dietary antioxidants.
- Describe the evidence for exogenous antioxidants to support anti-inflammatory clinical goals.
- Clarify the various roles antioxidants play as hormetic agents.
- Identify research gaps and challenges for the next generation of antioxidant research.

Methods

Literature Search

In conjunction with librarians at our institution, PubMed and Scopus database searches were conducted in the Spring of 2022 to gather a subset of medical literature articles describing the relationship between dietary antioxidants, hormesis, and chronic disease. The search strategy (Table 1) was adapted for each individual database and incorporated both subject terms and free text terms, as applicable. Additionally, snowballing was used when articles contained relevant citations. Five batches of articles were generated using PubMed or Scopus search terms.

Batch 1, 2, and 3 gathered articles discussing the relationship between hormesis, plant antioxidants, and human health. Batch 3 was a refined Batch 1 search to focus more on human studies. Batch 4 was a PubMed search created to examine the broader concept of whether antioxidant intake is linked to positive health outcomes in humans. Finally, Batch 5 was a PubMed search to identify randomized controlled trials using surrogate biomarker endpoints to identify the mechanistic role of antioxidants in humans.

Search Strategy

A total of 343 articles were collected from Batch 1, 2, and 3. After removing duplicates, 218 unique articles remained. All titles and abstracts were screened, and 66 articles were removed because they were commentaries or not focused on hormesis (Figure 1).

Data Abstraction

All articles were independently reviewed by two researchers; first, via title and abstract and then classified as review or non-review articles. Review articles were then examined to determine whether results from human studies were discussed. If the review reported most findings from trials in humans, it was marked with a "review focused on human results" tag to be used primarily as background. The non-review articles were tagged either with a human, cell, animal, plant, or other organism label depending on the model used for the study. For example, if human liver cells were used, then the study

Table 1. Search Terms Used for Each Batch.

Batch	Search Terms	# Of Results	Purpose
1 PubMed date: through 6/2022	(Hormetic response*[tiab] OR hormesis[tiab] OR hormesis[MeSH]) AND (plant-derived antioxidant*[tiab] OR plant antioxidant*[tiab] OR Polyphenols[tiab] OR Polyphenols[Mesh] OR phenolic acids[tiab] OR Flavonoids[tiab] OR Flavonoids[Mesh] OR Anthocyanins[tiab] OR Anthocyanins[Mesh] OR Lignans[tiab] OR Lignans[Mesh] OR Stilbenes [tiab] OR Stilbenes[Mesh] OR Carotenoids[tiab] OR Carotenoids[Mesh] OR xanthophylls[tiab] OR Xanthophylls[Mesh] OR Carotenes[tiab] OR vitamin E[tiab] OR vitamin E[Mesh] OR vitamin A[tiab] OR vitamin A [Mesh] OR vitamin C[tiab] OR ascorbic Acid[Mesh])	143	Hormesis
2 Scopus date: through 6/2022	((TITLE("Hormetic response*" OR hormesis) OR ABS("Hormetic response*" OR hormesis))) AND ((TITLE("plant-derived antioxidant*" OR "plant antioxidant*" OR polyphenols OR "phenolic acids" OR flavonoids OR anthocyanins OR lignans OR Stilbenes OR carotenoids OR xanthophylls OR carotenes OR "vitamin E" OR "vitamin A" OR "vitamin C") OR ABS("plant-derived antioxidant*" OR "plant antioxidant*" OR polyphenols OR "phenolic acids" OR flavonoids OR anthocyanins OR lignans OR Stilbenes OR carotenoids OR Xanthophylls OR carotenes OR "vitamin E" OR "vitamin A" OR "vitamin C")))	107	Hormesis
3 PubMed date: through 6/2022	(("Hormesis"[MeSH terms] OR "hormetic response"[All fields]) AND ("vegetables"[MeSH terms] OR "edible plants"[All fields] OR "food"[all fields] OR "antioxidants"[All fields] OR "polyphenol"[All fields] OR "resveratrol"[All fields])) AND (humans[Filter])	93	Hormesis
4 PubMed date: through 2021	(("antioxidants"[MeSH terms] OR "polyphenols"[MeSH terms] OR "lycopene"[MeSH terms] OR "resveratrol"[MeSH terms] OR "carotenoids"[MeSH terms]) AND ("disease"[MeSH terms] OR "chronic disease"[MeSH terms] OR "alzheimer disease"[MeSH terms] OR "neoplasms"[MeSH terms] OR "heart diseases"[MeSH terms] OR "mortality"[MeSH terms] OR "diabetes mellitus"[MeSH terms] OR "hypertension"[MeSH terms] OR "stroke"[MeSH terms] OR "obesity"[MeSH terms] OR "arthritis"[MeSH terms] OR "lung diseases"[MeSH terms]) AND "diet"[MeSH terms]) AND ((meta-analysis [Filter] OR randomizedcontrolledtrial[Filter]) AND (humans[Filter]))	273	Correlation between antioxidants and chronic disease
5 PubMed date: through 2021	(polyphenols[mesh] OR carotenoids[mesh] OR curcumin[mesh] OR resveratrol[mesh] OR ascorbic acid[mesh] OR flavonoids[mesh]) AND (food[mesh] OR diet[mesh] OR dietary supplements[mesh]) AND biomarkers[mesh] AND ((y_10[Filter]) AND (randomizedcontrolledtrial [Filter]) AND (humans[Filter]))	274	RCTs about antioxidants and biomarker endpoints

was tagged with a "Cell" label. A third researcher served as a tiebreaker if necessary.

Data Analysis

Statistical tests were tabulated in Excel.

Results

Of the 343 articles reviewed, 152 articles met the inclusion criteria, of which 40.1% (61/152) were review articles. Human results were the focus of 3 of the review articles (4.9%, 3/61). Most of the included studies were not reviews (59.9%, 91/152). Of the non-review articles, 2.2% (2/91) were performed in humans, 30.8% (28/91) in cell culture, 6.6% (6/91) in animals, 42.9% (39/91) in plants, and 17.6% (16/91) were in other organisms such as *Caenorhabditis elegans* or *Drosophila melanogaster* (Figure 2). Most of the non-review articles were studying cell or plant models (73.6%, 67/91) vs human or animal models (8.8%, 8/91).

Discussion

While numerous papers include antioxidants in their list of hormetic agents along with caloric restriction, physical exercise, and fasting, we found that most studies investigate hormesis in cell or plant models rather than in humans. This is consistent with a 2020 review describing the dose-response induced by phytochemicals that found, of included articles, 88% used cell culture models and only 2% used rodent models.[23] We build off this review paper by identifying barriers that limit research in

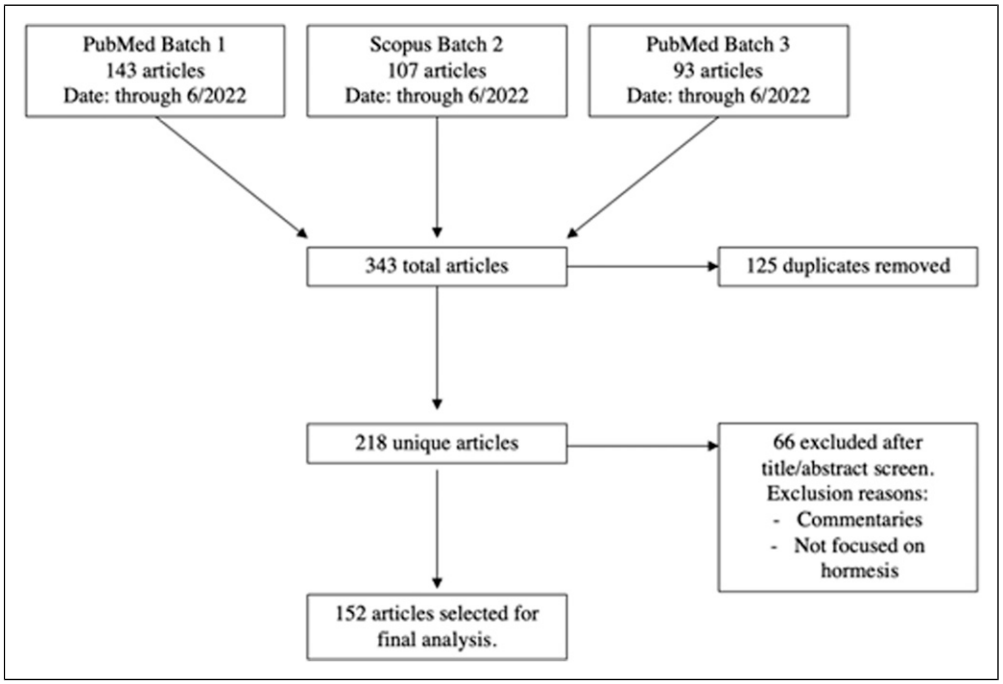

Figure 1. Flow diagram of articles included in the analysis.

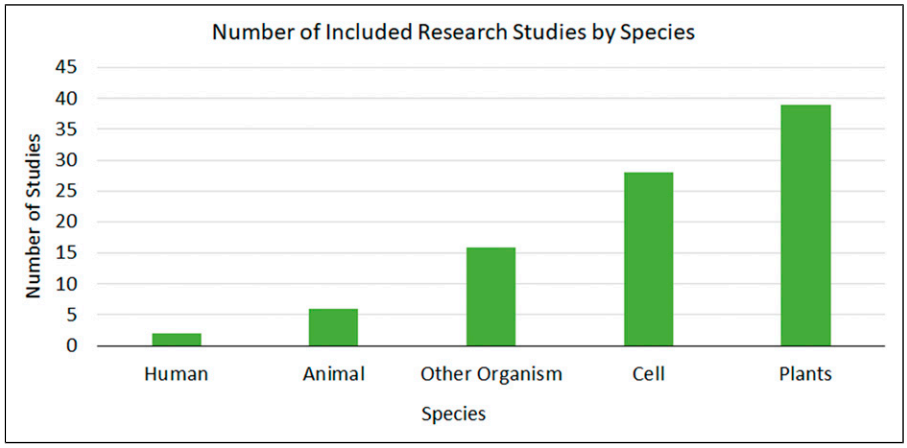

Figure 2. Included research studies by species. Human: 2/91 (2.2%). Animal: 6/91 (6.6%). Other organism: 16/91 (17.6%). Cell: 28/91 (30.8%). Plants: 39/91 (42.9%).

humans and provide a discussion of ways to transcend these obstacles.

We identified only 2 studies examining hormesis in relation to humans. The first investigated the effect of alcoholic beverages on in vivo plasma antioxidant activity. One drink of red wine, lager, or stout (alcoholic and alcohol free) increased plasma antioxidant activity while 3 drinks increased plasma pro-oxidant activity.[24] The pro-oxidant effect after consumption of 3 drinks was thought to result from the production of free radicals from ethanol metabolism. Therefore, less alcohol consumption would lead to less ethanol metabolism likely producing fewer free radicals. The framework utilized in this study may be valuable for future researchers to investigate antioxidant concentrations in humans after consumption of plant foods. Moreover, the second, a double-blind, randomized, placebo-controlled study, tested high (25 mg/d) and low (5 mg/d) dose supplementation with hydroxytyrosol (a polyphenol) on the induction of phase 2 enzymes in humans.[25] Results showed an insignificant difference of expression of most phase 2 enzymes in peripheral blood mononuclear cells between any group. Additionally, there was no significant difference between cardiovascular surrogate markers or inflammatory markers except for plasma hs-CRP and urinary isoprostanes. This study is likely underpowered due to a small sample size (n=21) and the use of a Latin square design,

which limited the window between the start and end of treatment to 7 days. The short treatment duration likely minimized the effect size, amplifying the lack of power.

Hormetic Responses in Cell Culture

Although cell culture models are incapable of capturing the complexity of mammalian physiology, they do provide a platform to conduct high throughput experiments capable of uncovering molecular mechanisms and other important concepts regarding phytochemical induced hormesis. A seminal 2010 review by Calabrese et al. described the dose-dependent effect of resveratrol on numerous cell lines, which included both healthy and cancerous tissues.[26] Generally, in human tumor cell lines, low doses of resveratrol enhanced cell proliferation in the range of 30%–60% while high doses suppressed cell proliferation. This result supports the potential use of high doses of resveratrol, attainable through nutraceuticals, and fits within one definition of hormesis whereby high doses create the opposite physiological effect of low doses but not another definition whereby low doses are beneficial and high doses are harmful (Calabrese et al., 2010). This is all assuming that these polyphenols can be made bioavailable. Furthermore, in non-tumor endothelial cell lines, low doses of resveratrol enhanced reendothelialization and improved cell migration whereas high doses, in contrast, were associated with a suppression of tissue repair and cell migration.[26] In non-tumor immune cells, low doses of resveratrol enhanced the response of multiple immune cells (e.g. T-cells and spleen cells) while the response was suppressed at high doses.[26] Whether the low-dose effect is harmful (cancer cell lines) or beneficial (non-cancer cell lines) to overall health, it is uncertain if the outcomes are clinically meaningful or negligible; future research (in animals and/or humans) will help clarify this. Additionally, this review concludes with the important observation that low doses of resveratrol exhibit either beneficial or harmful effects depending on the endpoint of interest. As discussed above, low doses increased tumor cell proliferation, which would negatively affect health. This contradicts one prevailing definition of hormesis, which states that low dose stimulation is beneficial to the organism. Future investigators must keep this in mind when defining hormesis and rationalizing results for low and high doses concentrations.

A review focusing on neural stem cell models for curcumin-induced hormesis found a hormetic-like, biphasic dose-response relationship for cell proliferation across 4 studies that used different lineages of neural stem cells.[27] Researchers hypothesized the increase in cell proliferation was due to curcumin-induced activation of p38 MAP kinase and MEK/ERK. Curcumin has also displayed hormetic features across numerous cell types and endpoints including supporting wound healing in human skin fibroblasts, suppressing inflammation in buffalo granulosa cells, stimulating heme oxygenase-1 (HO-1) activity in astrocytes, and many more.[27] It is well established that, at least in cell culture models, curcumin induces dose-dependent, bi-phasic effects across many domains. The next step in characterizing the hormetic response of curcumin is moving research to animal and human models.

Hormetic Responses in Animals

Experimental animal models provide us an opportunity to evaluate the dose-dependent effects of phytochemicals in a robust, in vivo setting—higher order research than in vitro cell culture models. One study investigated the cardioprotective effects of resveratrol in mice hearts exposed to ischemia. Animals were first treated with resveratrol at doses of 2.5, 25, and 100 mg/kg daily for 21 days. Then, ex vivo heart ischemia was followed by 2 hours of reperfusion, during which left ventricle function was evaluated. At 60 and 120 minutes, hearts exposed to low dose (2.5 and 25 mg/kg) resveratrol had improved aortic flow and left ventricular developed pressure compared to controls while ventricular function was significantly reduced with high dose (100 mg/kg)—perhaps indicating a U- or J-shaped dose-response curve.[28] The differing effects of low dose (positive effect) and high dose resveratrol inhibition (negative effect) is symbolic of the hormetic response. A similar trend was observed when researchers measured infarct size in rat hearts; high dose resveratrol (100 mg/kg) was associated with a larger infarct size whereas a low dose (2.5 mg/kg) with smaller infarct size.[28] A related study aimed to understand the cardioprotective effects of curcumin on myocardial damage in rat hearts and found low doses (100 and 200 mg/kg) prevented myocardial damage while a high dose (400 mg/kg) enhanced myocardial deterioration.[29] Of note, the dosing for these studies varies greatly between exogenous antioxidants with the high dose of one (resveratrol) being the low dose of another (curcumin); there is no broadly applicable dosing of exogenous antioxidants.

Furthermore, a review describing the dose-dependent effects of a mixture of green tea polyphenols (GTP) in rodents found medium and low dose GTP diets (0.01% - 0.1%) inhibited rat colon carcinogenesis while high dose did not.[30] Additionally, a similar result was also observed when looking at the effect of GTP on hepatic function in rodents exposed to dextran sulfate sodium (DSS). GTPs reduced DSS induced damage at doses of 0.01% and 0.1%.[30] The review concluded that low and medium doses (0.01% - 0.1%) of GTPs are beneficial via mitigating intestinal inflammation and carcinogenesis.[30] GTPs were hypothesized to minimize DSS induced hepatotoxicity and nephrotoxicity via modulation of self-protective enzymes. Of note, Murakami et al. cited a 1997 epidemological survey of over 85,000 females who consumed over 10 cups of green tea daily and had a protective effect on cancer risk, which further underscores the importance of distinguishing between dietary intake and supra-physiologic doses (2014).

Another example of hormetic response to exogenous antioxidants is the carcinogenic dose-response relationship exhibited by dietary caffeic acid in the forestomach and kidney of mice and rats. Researchers were interested in measuring how varying concentrations of caffeic acid affected cell proliferation in these model organisms. Rats were fed caffeic acid at concentrations of 0, 0.05, .014, 0.40, and 1.64% over the span of 4 weeks, and forestomach cell proliferation, a hallmark of carcinogenesis, was measured. The 0.14% arm showed a 30% decrease in the number of cells/mm while the 0.40% group displayed a 2.5-fold increase in cells/mm.[31] The authors concluded that the delayed cell division at low caffeic acid concentrations may reflect a protective cancer effect while the high dose accelerated cell growth may promote cancer.[32]

Translation Challenges

The examples in animal and cell culture models demonstrate that hormetic responses induced by exogenous antioxidants exist, which strengthens the likelihood that a similar result may be observed in humans (mechanistic plausibility). If true, this may have important implications for supplement use by the public as well as how clinicians utilize exogenous antioxidants in clinical practice. However, we must be careful when extrapolating results to humans due to the numerous complexities of the human body and human experience. For one, cell culture utilizes isolated cells stripped from their natural environment, which does not recapitulate the many interactions between cells in the ecosystem of the human body. Thus, many signals that occur in vivo are likely missing in cell culture experiments. In addition, when an agent is introduced into cell culture, it is typically placed in the media surrounding the cells. This is vastly different than how cells in the human body would be exposed to a compound entering through the GIT, as it would for food or dietary supplements. Cell culture also eliminates the role of bioavailability and its impact on dose exposure.

While it is less intuitive, it is clear that even animal models may be a poor predictor of outcomes in humans. Each animal has its own set of underlying genetics, anatomy and physiology, pathological responses, habitat, microbiome, and much more that influence how it responds to certain stimuli.[33] Thus, an outcome in one species may not translate to humans or even a different more similar species.[34] Other characteristics that limit translation of some animal model findings to humans include inadequate study design (e.g. insufficient power, limited representation of interindividual variability), failure to measure outcomes over a long duration, insufficient description of statistical tests, and limited reproducibility of intra- and inter-experimental results.[35] In summary, *results from cell culture and animal models may guide our investigations in humans but should not be a stand in for human data, as they sometimes are when data in humans is lacking* (with the exception of when human data is unethical or unattainable).[34]

Moreover, as of June 2022, there were no clinical trials listed on that were tagged with the term "hormesis;" therefore, it is uncertain when human results will be available. There are numerous examples of hormetic dose responses from the toxicology literature described in a hormesis database, which compiles over 5600 dose-response relationships across 900 agents.[32] Although the database provides a comprehensive analysis of hormetic responses through the lens of toxicology, we were unable to use it to advance our knowledge of exogenous antioxidant induced hormesis in humans because the database contains results from human models that are "generally in vitro." This agrees with our analysis of the literature that there are few to no studies utilizing in vivo human models.

Our review of the current state of the literature regarding the impact of exogenous antioxidants as hormetic agents on chronic disease reveals *limited discussion around a hormetic bi-phasic response and an inconsistent nomenclature that impacts the ability of the community to identify and locate the research*. The last expert review on this topic was compiled by Mark Birringer in 2011,[21] and the last literature review was done in 2005 by David Lindsay.[36] A 2020 systemic review in the Journal of Clinical Medicine by Jodynis-Leibert and Kujawska reveals little progress in the application of the hormetic response within animal models, let alone the complexity of human biochemistry, based on their analysis of the literature from 1990-2019.[23] Thus, given the limitations of extrapolating the impact of exogenous antioxidants on plants or in vitro, *the research community must shift the focus onto the role of exogenous antioxidants as hormetic agents within the complexity of human biochemistry in vivo*.

Opportunities and Challenges to Shift Exogenous Antioxidant Research into Humans

Subsequently, we offer insight into some of the existing barriers within the literature discussing hormesis and ways the research community may proceed to study nutritional hormesis in humans.

Lack of Precision in Data Collected on Dietary Sources of Exogenous Antioxidants and the Associated Absorption into the Human Body

The study of nutrition does not lend itself easily to many of the research approaches that have provided clarity in other areas of medicine such as pharmaceuticals. Many factors contribute to this difficulty including the complexity of food and the difficulty in creating blinding opportunities; how do you blind subjects to eating an apple or not? Several limitations in data collection were highlighted in our literature review related to the accuracy in measuring dietary intake of exogenous antioxidants and the ability to quantify the amount of antioxidant delivered to cellular targets (the bioavailable dose).

One common weakness of many studies is the use of inexact food measurement tools such as food frequency

questionnaires, 24-hour recalls, or food records.[37] One possible solution is to use a controlled diet environment that would allow complete control over intake for the duration of the study. This would ensure higher accuracy in the amount and type of dietary antioxidants consumed. However, the increased cost of such studies in terms of research dollars and participant burden must be weighed against the benefit from increasing data accuracy, which we feel is warranted to establish precise thresholds that will allow us to understand when a dose-response relationship goes from beneficial to harmful. Once this aspect of the data is more precise, the question of dietary antioxidant bioavailability can be addressed.

The bioavailability of nutrients is the amount of the nutrient that makes its way through the digestion and absorption process such that it becomes available to support use or storage in the body.[38] Nutrients, including exogenous antioxidants, enter the body through a selective process in the GIT, digestion and nutrient absorption. *Setting a dose-response threshold requires increased specificity to acknowledge the factors involved in the digestion and absorption of dietary nutrients in the GIT.* Thus, the use of blood biomarkers that represent dietary antioxidant bioavailability rather than or in conjunction with dietary patterns may greatly improve the precision and accuracy of the research in this field.

Factors that impact digestion and absorption and ultimately bioavailability of exogenous antioxidants include[39]:

Medications. The side effects from medications extend into the microbial composition of the intestines and alter the environment in which exogenous antioxidants interact with oxidants and their bioavailability. Antibiotics as well as many non-antibiotic drugs predictably alter the microbiome towards pro-inflammatory functionality.[40] Thus, the current and former medical history of a patient may alter the behavior of the dietary antioxidant within their specific microbial terrain, which would alter the hormetic threshold.

Age. Changes to the GIT associated with aging negatively impacts the function of the GIT, which alters the ability to digest and absorb nutrients including exogenous antioxidants.[41] Thus, the dose of exogenous antioxidants that a person is able to access from a dietary source (bioavailability) varies greatly depending on the health of their GIT. Age is an independent risk factor for impaired gut function. In addition, age-related changes to the immune system (immunosenescence) result in an increase in the amount of pro-inflammatory messengers produced, which leads to states of higher oxidative stress.[42] Given that the majority of immune cells reside in and around the GIT, immunosenescence likely changes the reaction to oxidative stress due to age alone.

Food. Variability in nutrient concentrations within a food due to the health of the environment (soil/air/water), farming practices, time from harvest, and method of preparation changes the quantities of exogenous antioxidants within any given food.[43,44] Crinnion's study comparing food value between organically and non-organically grown produce confirms that food grown organically contains significantly more exogenous antioxidants than their non-organic counterparts at least in some cases.[44]

Gastrointestinal Tract Function and the Microbiome. Digestion consists of bioaccessibility and absorption. Bioaccessibility is the liberation and solubilization of food components—getting the nutrients out of the food. Absorption is getting those now free nutrients transported across the gut barrier. Both bioaccessibility and absorption play key roles in bioavailability. The gut microbiota—bacteria, archaea, yeast, fungi, viruses, and phages that comprise the gut microbiome—also play a very important role in bioaccessibility and therefore bioavailabilty; for instance, up to 10% of energy requirements come from energy harvest by the gut microbiota.[45-48] A specific instance of this has been elegantly shown through a resistant starch feeding study in which *Ruminococcus bromii* was required to be present in the gut microbiomes of participants for complete utilization of the resistant starch (100% with vs 20%–30% without *R. bromii*).[49] This alludes to the large interindividual variability of microbiomes and, thus, functional outcomes such as bioaccessibility, which has been shown throughout the literature.[48,50-52] How does this role in bioaccessibility and therefore bioavailability affect polyphenols? An estimated 90% of polyphenols in food make it to the gut microbiome unprocessed, where the microbiota processes them and improves bioavailability for the host.[53-56] Therefore, the dose-response relationship of polyphenol intake is likely powerfully modified by the composition and/or function of the gut microbiome; this has all but been overlooked to date.

Consensus is lacking on how to assess exogenous antioxidant and oxidants in human models in order to understand the effect of dietary antioxidants on oxidative stress

The methods used to assess antioxidant concentrations vary widely and prevent a more detailed understanding of dose response. It is unclear which biomarkers are the most reliable measure of total antioxidant concentrations and which we should look to for an understanding of oxidative stress. Should we use plasma concentrations of antioxidants or oxidants? Should we look at the Total Antioxidant Capacity of a food or nutrient? Should we assess oxidative stress using C-reactive protein (CRP), homocysteine, or lipid peroxides? Should we use a combination of these? If we can develop standards of measurement for antioxidant activity and oxidant exposures, we can apply these standards to all antioxidants to elucidate the impact on oxidative stress. Another variable that

adds complexity is that distinct antioxidants have different properties and occupy unique roles. For example, some are lipid soluble (e.g. vitamin E) and others are water soluble (e.g. vitamin C), which makes it unclear whether various antioxidants will work with, against, or disregard one another *in vivo*[57] Perhaps standard methods could be developed by the National Institute of Standards and Technology (NIST) in conjunction with leaders in the field, developing a standardized methodology as well as language. This would allow for easy data harmonization and comparison across multiple studies, which will be necessary to gain a complete understanding of this complex relationship.

Lack of standardization in research approach erodes the impact of cumulative research

Study Populations Unclear. When reviewing the literature, we sought to identify hormetic responses found in human subjects. In our literature search, 40.1% (61/152) of included reports were review papers. Review papers, by nature, combine results from many different studies; thus, data from multiple types of subjects (e.g. cell culture and animal models) is described together. In many cases, we found it challenging and cumbersome to pinpoint the subject of particular data points without examining the provided reference, meaning the science is not being communicated precisely enough in current reviews of the evidence. Some review papers did describe the subject of the research for all items of evidence; however, this was not universal and is an area for improvement for the field.

Lack of Keyword Standardization. All 4 non-review studies previously discussed in the animal section were not captured in our initial search.[28-31] It is unclear exactly why these articles were excluded; however, 3 of 4 were tagged with the keyword, "Dose-Response Relationship, Drug" and not "hormesis," which was used in our search. The absence of universal keywords by all articles discussing hormesis is potentially limiting when attempting to identify relevant literature.

Throughout our review process, we encountered keywords used inconsistently and interchangeably across research papers, which made it difficult to discern the precise meaning and scope of the research. Key terms that would benefit from standardization in the field are listed in Table 2. Our review process was bogged down by crucial key words such as antioxidant and polyphenol, being used with alternative meanings that were not applicable across research papers. For example, the key word 'Antioxidant' is defined by the National Center for Complimentary and Integrative Health as either man-made or natural substances that have a positive effect on the health of the cell. This definition is sufficiently broad that it could include nearly all vitamins, minerals, and fatty acids that are involved in the maintenance of the cell as well as non-nutritive plant phytochemicals. Thus, clarity would increase with the consistent use of specific qualifiers such as including the word 'phytochemical' before antioxidants to narrow the topic to exclude man-made substances. The group of researchers from IntechOpen in their chapter on *Antioxidants Categories and Mode of Action* further categorize the field by narrowing the topic to enzymatic vs non-enzymatic antioxidants, which distinguishes between antioxidants that catalyze reactions (Superoxide dismutase, Glutathione peroxidases, and Catalase) and those that contain hydroxyl groups that scavenge free radicals throughout the body (vitamin C, vitamin E, B-carotene, phenols, tannins, terpenes).[58] Research terms that can be specific and descriptive will help narrow the focus and allow more meaningful consolidation of research in the field. For example, rather than using the broad term 'antioxidant,' employing qualifiers with this term such as nonenzymatic phytochemical antioxidants.

Confusion About Whether or Not Exogenous Antioxidants can be Toxic

Some observational studies challenge the notion that there is an upper limit for exogenous antioxidant utility by showing a positive correlation between increased exogenous antioxidant intake and better outcomes. Data from the PREDIMED trial showed reduced all-cause mortality for the highest polyphenol intake (self-reported) compared to lowest intake via multivariate analysis.[65] Moreover, a clinical trial investigating the impact of carotenoids on breast cancer recurrence reported that women with the highest plasma carotenoid concentration had a significantly reduced risk of breast cancer incidence.[66] This trend is not isolated to these particular studies. Various meta-analyses of observational studies also found a reduction in adverse health events with increased exogenous antioxidant intake[67-70] or circulating concentrations of antioxidants.[71]

Although the general trend of higher intake and favorable outcomes is described for various types of exogenous antioxidants in meta-analyses, conflicting results exist that impart reasonable doubt into the assumption that greater consumption of exogenous antioxidants is always beneficial. For example, a fertility study by Dias et al. showed a decline in sperm viability (a distinct U-shaped curve) after an initial positive impact at lower doses of exogenous antioxidant intake likely due to the inhibition of essential signaling pathways that ROS trigger, which creates homeostatic balance.[72] Furthermore, a meta-analysis found a U-shaped, dose-response relationship between dietary vitamin C and all-cause mortality.[68] Although unclear why, it is possible that high doses of vitamin C in the presence of transition metals serve as pro-oxidants. The same meta-analysis found a U-shaped association between circulating lycopene and all-cause mortality. The authors suggest that circulating lycopene

Table 2. Key Words Found to be Used Inconsistently and Interchangeably Across the Literature.

Vocabulary Used	Definition	Types
Antioxidant	Antioxidants are man-made or natural substances that may prevent or delay some types of cell damage.[59]	Vitamin C, vitamin E, plant polyphenol, carotenoids, and glutathione are nonenzymatic antioxidants.[60]
Polyphenol	Polyphenols are secondary metabolites of plants and are generally involved in defense against ultraviolet radiation or aggression by pathogens. More than 8000 polyphenolic compounds have been identified in various plant species. All plant phenolic compounds arise from a common intermediate, phenylalanine, or a close precursor, shikimic acid.[61]	Phenolic acids Flavonoids Stilbenes Lignans
Plant-based antioxidants	Plant-derived antioxidants are a large group of natural products with reducing or radical-scavenging capacity.[62]	Non-plant-based antioxidants are synthetically derived for use in food preservation
Phytonutrients	Phytonutrients is a broad name for a wide variety of compounds produced by plants… Some researchers estimate there are up to 4000 phytonutrients.[63]	Antioxidants, flavonoids, phytochemicals, flavones, isoflavones, catechins, anthocyanidins, isothiocyanates, carotenoids, allyl sulfides, polyphenols
Phytochemical	Phytochemicals can be defined, in the strictest sense, as chemicals produced by plants. However, the term is generally used to describe chemicals from plants that may affect health but are not essential nutrients.[64]	From LinusPauling institute[64]: Carotenoids, chlorophyll and chlorophyllin, curcumin, fiber, flavonoids, garlic, indole-3-carbinol, isothiocyanates, lignans, phytosterols, resveratrol, soy isoflavones From antioxidants, 2019[60]: Flavonoids, catechins, carotenoids, carotene, lycopene, and herbs and spices such as diterpene, rosmariquinone, thyme, nutmeg, clove, black pepper, ginger, garlic, curcumin, and derivatives

may be a surrogate for intake of highly processed tomato products such as sugar-sweetened ketchup or pizza sauce, which contain high amounts of lycopene. If true, the negative results found for high levels of circulating lycopene may be due to harmful effects of ultra-processed foods rather than lycopene itself.

In summary, *there is uncertainty about the optimal dose of exogenous antioxidant intake. Clear toxicity limits to exogenous antioxidants have not been well established and are likely dependent on the particular antioxidant in question.* Outside of supplements, antioxidants are almost universally found in foods, creating unavoidable confounding. Food exerts its effects through multiple interactions between the phytochemicals it contains and biochemical processes in the human body—and the gut microbiome. This factor further complicates the equation. We may not be able to tease apart which items within a food are causing harm and which are promoting health easily or, perhaps, even at all. Further, the entourage or food matrix effect is elucidating that foods are not simply the sum of their parts, meaning that any one component in isolation may not exhibit the same effect as it would in a whole food.

Studies do not Consider the Importance of the Duration of Exposure to a Dose of Exogenous Antioxidants

Hormesis is typically studied by introducing a pre-set dose or series of doses of a compound to either a cell or animal model, followed by observing a response, often immediately or shortly thereafter. This design allows researchers to determine the dose-response relationship of the system and compose curves to illustrate the correlation. Although this results in valuable data, it may be equally important to appreciate the temporal trends of a dose-response curve. For example, a stimulatory, low dose may only be beneficial if applied for a short amount of time. A longer duration could potentially elicit harmful effects on the system. In contrast, a high dose seen for a short period of time (i.e. immediately after a meal) may not be detrimental due to its transitory nature. Even though this is a theoretical situation, it provides a framework for how time may affect a hormetic response. This is especially important to consider when investigating hormetic phenomena in humans because of the complex interplay between compounds we ingest and the cells within the body. Therefore, we propose use of area under the curve (AUC) instead of simply dose. Time in range could also be potentially beneficial in the future once hormetic relationships have been established.

Bioindividuality Has Not Been Fully Acknowledged From A Genetic and Epigenetic Perspective

The genetic blueprint that an individual patient overlays onto the bioavailability of antioxidants will create variation in the dosing of exogenous antioxidants from dietary and supplemental sources. Smoliga, Baur, and Hausenblas make note of the "inter-individual difference in bioavailability" in their

2011 review of clinical trials investigating resveratrol.[73] Single Nucleotide Polymorphisms (SNPs) such as selenoprotein P (SEPP1) and glutathione peroxidase 1 (GPX1), impact antioxidant bioavailability by changing the transport, receptor levels, and enzymatic activity.[74] Using nutrigenomics in the clinic requires additional insight into how an individual's genetic and epigenic profile will require personalization of any therapeutic recommendations. While the promise of personalized and precision nutrition including nutrigenomics are great, we are not there yet. To build the evidence base, the National Institutes of Health is launching the Nutrition for Precision Health study, powered by the All of Us Research Program (Nutrition for Precision Health).[75] While antioxidant hormesis is not a stated objective of this research program, it may lead to a large human data set in which this relationship can be explored.

The changing Definition of Hormesis Makes it Difficult to Compare Research Results

We found that the definition of hormesis varies depending on the area of study, the timeframe of study completion, and the preference of the study authors (Table 3). Further, the cultural understanding of hormesis adds to the confusion around what exactly a hormetic response looks like and whether or not a given compound or lifestyle behavior exhibits this pattern. In summary, the field of nutrition lacks a cohesive and agreed-upon definition of hormesis that would provide a clear standard by which antioxidant behavior patterns may be judged.

Improved Study Design can Bring Consistency with Cumulative Effects Across Studies

We observed a lack of consistency in study design and application across different types of exogenous antioxidants, making it difficult to aggregate findings across research papers. As a foundation for employing cumulative research, attention needs to be applied to systematically studying each antioxidant to define the oxidant-resolving patterns as oxidant scavenging (linear curve), hormetic (J- or U-shaped curve), or possibly a hybrid of the two.

Distinguishing the Impact of Specific Antioxidants Can Inform Antioxidant-Specific Guidelines

Frequently, exogenous antioxidants are lumped into a group and discussed as if there was a homogenous response to stimuli and doses; however, the actions of specific antioxidants vary greatly from one another. The subclasses of exogenous antioxidants include enzymes, vitamins, minerals, fatty acids, plant phytonutrients, and synthetic compounds. Even within the various subclasses of plant phytonutrients that are classified as antioxidants a vast array of structure and function exist. For example, there are over 8000 polyphenols that have been identified in plants, each with their own chemical structure and metabolic target.[58] Thus, to group all of these into larger classes risks losing the specific details that allow clinicians to target nutrient therapy to the desired mechanism of action that will address imbalances at the very root of disease.

Strengths and Limitations. This review has 2 major strengths and 3 major limitations. First, the strengths. We searched 2 large databases and found articles discussing the relationship between plant antioxidants and hormesis. Our results were consistent with the general consensus of the literature, which is that hormesis has been rarely studied in human populations. In addition, we offered actionable advice for researchers and the field for future experiments exploring the hormetic responses in humans. Yet, this study has limitations. Our initial search did not include the terms "dose-response," which we found later was a keyword tagged by many of the articles discussing hormesis. We may have missed articles that found a hormetic response but did not tag their report with the keyword, "hormesis." Furthermore, our initial aim was to summarize our current knowledge of the hormetic dose-response relationship induced by plant-based antioxidants in humans; however, our literature search revealed very limited data on

Table 3. Studies Using Different Definitions of Hormesis.

Author	Date	Definition	Subject Area
DP Hayes (Hayes, 2007)	2007	The biphasic nature of the U-shaped response can… be subdivided into low and high-dose regions where the toxicity response differentially occurs (the arms of the U), plus a region of no toxic effect (the trough of the U)	Nutrition
Calabrese (Calabrese et al., 2010)	2010	Hormesis is a biphasic dose response phenomenon that is characterized by a low-dose stimulation and a high-dose inhibition	Toxicology
Chirumbolo (Chirumbolo, 2011)	2011	A biphasic dose–response relationship for which low doses display stimulation and high doses inhibition	Toxicology
Jodynis-Liebert and Kujawska (Jodynis-liebert and Kujawska, 2020)	2020	The phenomenon in which a chemical is able to induce biologically opposite effects a different doses	Nutrition

this subject. Thus, we adapted our study and moved in the direction of offering advice to researchers on aspects we believe are important when studying hormesis in humans. Finally, our search terms were bound by the keyword 'hormesis'; thus, we did not capture all clinical trials that could have potentially found results consistent with a hormetic response. For example, a clinical trial investigating the efficacy of a supplement may have found a biphasic dose response curve. However, it is likely that the authors of such trials were more focused on efficacy of the supplement compared to placebo and therefore did not discuss the results within the context of a hormetic response. This article would not have garnered the keyword 'hormesis' or populated in our search. One would have to filter through all clinical trials investigating plant antioxidants and adjudicate whether the results fulfilled hormetic criteria to identify all instances of hormesis within this context. Therefore, limiting the proper application of findings, especially by clinicians.

Conclusions

Given the limited robust evidence, it is difficult for clinicians to ascertain the appropriate therapeutic dose of dietary antioxidants or, even more concerning, supraphysiological dosing of exogenous antioxidants in supplemental form. It is currently unclear how the two functional mechanisms of antioxidants (free radical scavenging and hormesis) cooperate in human biochemistry. The role of exogenous antioxidants as hormetic agents has been overwhelmingly studied in plants and cell culture, leaving clinicians blinded to the effects of these chemical messengers in their patients. Meta-analyses based on observational research establish an association between diets that are high in plant antioxidants with a reduction in chronic disease and improved well-being,[68,76,77] which may run contrary to the hormesis theory of antioxidants or be in keeping with the theory based on lower absorption and bioavailability. A knowledge gap exists between the observational human studies and the cell culture and animal model research, which shows a biphasic, hormetic quality to the role of exogenous antioxidants. Cell culture and animal model research cannot accurately be translated directly into clinical care; therefore, exogenous antioxidant therapy cannot be employed in the clinic at this time. The question remains, at what dose and/or blood concentration do polyphenols promote an anti-inflammatory response vs overwhelming the biological infrastructure and become pro-inflammatory? Our concern is that well-meaning clinicians as well as the public apply the thinking that more is better for exogenous antioxidants. In fact, some of the literature supports this approach; however, growing consensus supports the existence of a hormetic response, which challenges this concept. In summary, we have described why it is currently difficult to translate our understanding of hormesis to therapeutic antioxidant intake in humans and have proposed steps for the research community to address the knowledge gap between cells/animals and humans. A stronger understanding of the functions of exogenous antioxidants in humans will surely help tackle the chronic disease epidemic and improve the lives of patients.

Appendix

Abbreviations

AUC	Area under the curve
CRP	C-reactive protein
GIT	Gastrointestinal tract
GTP	Green tea polyphenols
NRF2-KEAP1	NF-E2 p45-related factor 2 - Kelch-like ECH-associated protein 1
ROS	Reactive oxygen species
SNPs	Single nucleotide polymorphisms
SEPP1	Selenoprotein P
GPX1	Glutathione peroxidase 1

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Author Contributions

JW and LAF designed research; LAF, JW, and BK conducted research; JW and BK analyzed data; JW, BK, and LAF wrote the paper. JW and LAF had primary responsibility for final content. All authors have read and approved the manuscript.

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Ethical Statement

Ethical Approval

This literature review was conducted in adherence to the highest ethical standards. Proper citation and attribution were maintained to uphold intellectual property rights and prevent plagiarism. The selection of

literature sources was based on relevance, quality, and contribution to the research topic, irrespective of authors' affiliations or personal beliefs. Conflicts of interest were disclosed and managed appropriately. Inclusion and diversity were valued, and efforts were made to incorporate a wide range of perspectives. The research methodology, search strategies, inclusion criteria, and data analysis techniques were transparently documented, promoting reproducibility. Continuous ethical reflection guided the entire research process.

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Data Availability Statement

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

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