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Recommending flavanols and procyanidins for cardiovascular health: Revisited

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ABSTRACT

The last 8 years have seen significant developments in our understanding of dietary flavanols and procyanidins in the context of human health and nutrition. During the same time, recognition of the importance of nutrition in primary disease prevention and health maintenance has increased. In addition, the concept of dietary bioactives (food constituents that although not essential to human life and procreation, may nevertheless play an important role in disease risk reduction, primary disease prevention, and healthy aging) has been created and developed. Applying assessment criteria specific to health maintenance and primary disease prevention, we aimed at broadly evaluating and discussing currently available data on flavanols and procyanidins, with an eye towards potentially advancing the future development of dietary guidelines and public health recommendations. Novel insights and advancements as well as current gaps and shortcomings in our understanding are identified and discussed. While centered on flavanols and procyanidins, the outcomes of this review may also have broader relevance for the further development of the concept of bioactives, and any future framework for the assessment of their role in human health and nutrition.

1. Introduction

Eight years ago, we published a paper in this journal in which we reviewed the then available data on dietary flavanols and procyanidins in the context of cardiovascular health and potential future dietary recommendations (Schroeter et al., 2010). Since that time, interest in the role that flavanols and procyanidins may play in health and nutrition has not declined. On the contrary, a considerable body of data has been generated, and some of the knowledge gaps identified in the 2010 review have since been addressed.

From today's perspective, there exist other significant trends and developments in nutrition and primary disease prevention that have an important bearing on any current reassessment of our initial question. For example, the general recognition of the importance of primary disease prevention and health maintenance as key enablers to improve health and quality of life, and to manage the ever-increasing health care costs for non-infectious and age-related diseases is generating an even greater role and higher expectations for nutrition (Weintraub et al., 2011; Yetley et al., 2017). Moreover, the general awareness of the impact on human health of the gut microbiome continues to increase, and calls for the development of evidence-based approaches aimed at providing personalized nutritional advice and diet-based solutions for maintaining and improving an individual's health status (Kau et al., 2011; Lynch and Pedersen, 2016). Key trends in this overall context also include the development of the concept of dietary bioactives, food constituents, which although not essential to human life and procreation, may nevertheless play an important role in disease risk reduction, primary disease prevention, and healthy aging (Office of Disease Prevention and Health Promotion, 2004). Many scientists and scientific bodies, representing a broad-range of disciplines, are currently engaged in a discourse aimed at further developing this concept, and to reach consensus around appropriate assessment frameworks that may be applicable for an evidence-based evaluation of the role of bioactives for human health (Ellwood et al., 2014; Lupton et al., 2014, 2016). Among other outcomes, this discourse

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also provides valuable insights with regard to need and usefulness of specific assessment criteria and, thus, represents an opportunity for reevaluating the assessment criteria applied in our 2010 review of flavanols and procyanidins.

Taken together, based on the data generated in the last eight years, and considering various larger trends and developments, we aim here at revisiting the topic of our initial inquiry into the role of dietary flavanols and procyanidins in human health and nutrition.

1.1. Assessment criteria

Based on a variety of guidelines and principles established by the scientific community and government organizations with regard to scientific as well as regulatory frameworks that underlie the development of public health messages and dietary recommendations (Biomarkers Definitions Working Group, 2001; CFSAN, 2009; Colatsky, 2009; Desai et al., 2006; EFSA, 2006; EFSA, 2018; FDA, 1999; Gobburu, 2009; Hill, 1965; IOM, 2010; Lathia et al., 2009; Pryseley et al., 2007; Spilker, 2009; Wagner, 2008; WHO, 2001; Williamson and Holst, 2008), we have previously derived and applied specific assessment criteria to our inquiry into the potential health benefits of flavanol/procyanidin intake (Schroeter et al., 2010). These initially selected assessment criteria are still largely pertinent, valid, and applicable. However, informed by the current discourse related to the question of how best to assess dietary bioactives in the context of health and disease risk reduction (Ellwood et al., 2014; Gaine et al., 2013; Lupton et al., 2014, 2016), we have, in part, revised and restructured the assessment criteria that will serve as the basis for the current review (Fig. 1).

2. Results

2.1. Is the food constituent/bioactive adequately defined?

A major limitation with regard to a meaningful comparative analysis and interpretation of data from dietary interventions and epidemiological studies in the context of bioactives generally, and flavanols and procyanidins in particular, is a certain lack of specificity and clarity when it comes to the characterization of the nature of a given intervention. That is, the precise composition of the test materials or the chemical identity of the specific compounds under investigation is not fully established or clearly communicated. Independent of questions related to analytical chemistry, there is no disagreement around the notion that a clear and consistently applied definition and nomenclature is key to all aspects of evaluating any bioactive in the context of human health (Fig. 2). However, the practical application of this insight is less consistent and is still fraught with the same technical as well as historic difficulties as in 2010. Now, as then, the terms often found in scientific communications are frequently based on the historic use of descriptors that were initially founded on either the source material (e.g. tea-, wine-, cocoa-, apple-, grape seed-, hawthorn-flavanols, etc.) or the intention to convey certain attributes or associations (e.g. tea-, wine-, berry-, cocoa-, etc. antioxidants, or polyphenols).

In the context of a health claim substantiation, EFSA (2012) adopted a previously developed definition for the term 'cocoa flavanols' (Hammerstone et al., 1999), as representing the sum of all flavanols and procyanidins present in cocoa that exhibit a degree of polymerization (DP) ranging from 1 to 10 (DP1-10). While seemingly straight forward and specific, the application and interpretation of this, and similar definitions, is often complex and not easily accessible to non-experts. Moreover, although more detailed and specific than many other source material-based terms currently in use, the definition for cocoa flavanols adopted by different researchers, and subsequently by EFSA, is on its own merit useful, but also insufficient. This definition does not define/quantify: (1) the relative abundance of individual components of DP1-10, i.e. the relative abundance of DP1 vs. DP2 or DP10, for example; (2) the absolute or relative abundance of individual compounds included under DP1, DP2, …DP10; or (3) the absolute or relative levels of specific stereoisomers present in DP1-10 (Fig. 3). While it may seem overly pedantic perhaps, based on currently available data on the biological effects of flavanols and procyanidins, this degree of detail would actually be required in order to speak to the biological efficacy and safety associated with the intake of the complex mixture that is 'cocoa flavanols.' If we were to imagine a cocoa flavanol-based dietary intervention trial with a double-masked, cross-over design, and a measure of cardiovascular function as primary outcome, we could easily picture the following situation: The testing of two different cocoa flavanol-based test materials, both adhering to the same definition for cocoa flavanols (i.e. sum of DP1-10), and both delivering the same intake amount, resulting in very different outcomes (e.g. one intervention leading to statistically significant improvements while the other does not). One explanation for such a seemingly surprising divergence in outcomes could lie in major differences between the two test materials with regard to the relative abundance of specific components within DP1-10. For instance, despite the fact that in the above example both interventions delivered the same intake amount of total DP1-10 cocoa flavanols, significant differences may exist in the relative respective abundance of (−)-epicatechin vs. (−)-catechin or DP1 vs. DP10. In this case, although the definition for cocoa flavanols was clear and consistently applied, and the intake amounts were the same for both groups, the outcomes would be expected to be very different, as there is evidence for significant differences in the absorption as well as the biological effects in humans of the specific compounds exemplified (Ottaviani, 2011; 2012a, Wiese, 2015). Consequently, solely based on the knowledge that cocoa flavanols were defined as the sum of DP1-10 will be insufficient for meaningfully interpreting and analyzing the outcomes of dietary interventions and

Assessment criteria to evaluate health benefits and nutrition relevance of bioactives

1. Is the food constituent/bioactive adequately defined?
2. Are there well established and validated methods for the analysis of the food constituent/bioactive in foods?
3. Are there sufficient data from adequate epidemiological investigations to establish a reasonably reliable habitual average intake amount and associations between the intake of the food constituent/bioactive and health?
4. Are there comprehensive data on the ADME of the food constituent/bioactive in humans?
5. Are there sufficient data from adequate prospective clinical dietary intervention studies demonstrating the efficacy of the food constituent/bioactive?
6. Are there adequate data demonstrating the general safety of the food constituent/bioactive?
7. Are the mechanisms of actions by which the food constituent/bioactive exerts its health benefits known and understood?
8. Are there systematic reviews and meta-analyses of the effect of the food constituent/bioactive?

Fig. 1. Assessment criteria to evaluate nutritional relevance of bioactives, including flavanols and procyandins, in the context of primary prevention and health. ADME: absorption, distribution, metabolism and excretion.

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