Abstract
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Flavonoids: Where We are and Where We Need to Go: Foods, Databases and Labels
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Flavonoids are phenolic compounds in foods that are among the most ubiquitous of the non-nutrient bioactive compounds with potentially positive health effects. At present no dietary reference intake exists for these compounds. Although our understanding is far from complete, their bioavailability, mechanisms of action, metabolism and their biotransformation in the human microbiome are now becoming clearer, as others will describe later in the symposium. Clearly the flavonoids differ in their bioavailability and also in their functional characteristics (Serrano, Puupponen-Pimia, Dauer et al 2012). Early epidemiological studies focused on the associations between a single food (such as tea) or a few foods (soy foods, or cocoa foods) rich in particular flavonoids and differences in health outcomes between Asian and Western populations. While some studies have reported health benefits, others have not. In part this may have been attributable to the large errors in estimating flavonoid intakes owing to incomplete information available about the types and amounts of flavonoids in foods. Alternatively it may be that the foods also possess many other bioactive compounds in addition to the flavonoids, which, when working together, have positive health effects. Of course it is also possible that they lack efficacy. Only more rigorous research will provide definitive answers on these issues.

Significant progress has been made in the past twenty years in developing and applying analytical techniques to characterizing and quantifying the flavonoids in foods. Databases on foods and dietary supplements are now complete enough to allow investigation of total dietary intakes of the flavonoid compounds and classes instead of relying solely on the contribution of a single food or foods rich in them. Large population-based cohort studies are now available with numbers large enough and populations diverse enough to permit assessment of the effects of flavonoid intakes and foods rich in flavonoids such as those from tea, cocoa and soy on health outcomes over time. While these advances are welcome, dietary assessment tools are still too crude to capture many of the details about foods that may influence their flavonoid content, and the flavonoid databases still lack the specificity about some of the compounds that may be necessary to fully characterize their biological effects. Tea is one of many such examples (Peterson, Dwyer, Jacques
et al 2004; Peterson, Dwyer, Bhagwat, et al 2005) The development of biomarkers of flavonoid intakes is therefore extremely important to advancing the field.

There is no dietary reference intake for total flavonoids or individual classes or compounds. A generally accepted paradigm for assessing and making dietary recommendations about non-nutrient bioactives is currently lacking, but some procedures will be needed if and when the beneficial health effects of these constituents are more definitively demonstrated. Whether quantitative recommendations should be for specific or total flavonoid intakes or rather more general statements should be made about foods rich in these compounds remains to be determined. It is likely that there are specific bioactive compounds that are linked to effects, rather than entire classes or flavonoids as a group.

Thanks to improvements in flavonoid databases and enhancements to dietary assessment tools, it is now possible to assess intakes of flavonoids in all classes in populations and to study their associations with health outcomes, although the quality of the cohort studies needs improvements in exposure assessment, valid surrogate markers of health outcomes and length of follow-up (Erdman, Balentine, Arab et al 2005; Peterson, Dwyer, Jacques et al 2012 in press). Clinical studies of specific flavonoids that are now possible with well characterized flavonoid ingredients. These will also be essential for assessing effects and testing interventions.

Scientific interest in flavonoids stems from the possibility that one or more flavonoid classes or compounds has beneficial effects in decreasing risks of chronic degenerative diseases such as cardiovascular disease, diabetes mellitus and certain cancers, as well as in contributing to bone health, cognitive function and weight management (De Bock, Derralk and Cuttfield 2012; Zomer, Owen, Magliano et al 2012, Shrive, Bauer, McDonald et al 2011, Hooper, Kroon, Rimm et al 2008, Tokede, Gaziano and Djousse 2011). Later in this symposium each of these topics will be discussed in depth, and recent symposia have also reviewed them (Williamson, Sies, Heber et al 2009). Since morbidity and mortality take many years if not decades to develop, and the effects of food flavonoids on physiological processes necessary for health are likely to be small but cumulative over time, validated intermediate markers of outcomes are critical in carrying out such studies. It is of interest that the beneficial effects observed do not seem to be limited to a single food, a single flavonoid, or a single class of flavonoids, at least for cardiovascular disease mortality (Mink et al 1976, McCullough et al 2012).

There is a great interest on the part of food producers about labeling their products and using health claims to describe the associations between consumption of foods or ingredients and beneficial physiological effects and health outcomes (Aggett, Hathcock, Jukes et al 2012). From the public health nutrition standpoint, the most appropriate way to label products depends upon what constituent(s) has health effects. For example for tea, is it total amount of polyphenols, total flavonoids, or catechins, or is it a combination of this with other bioactive compounds that are also
The US Food and Drug Administration, the UK Food Standards Agency, and the European Food Standards Agency (EFSA) and regulatory agencies in many other countries as well have developed regulations and procedures for permitting health claims. This usually involves generally acceptable scientific evidence, including evidence that the claimed effect of the food is beneficial to health; that there is a cause and effect relationship between consumption of the food and claimed effects in humans using generally accepted criteria (e.g., strength, consistency, temporal occurrence, specificity and evidence of a dose-response relationship as well as biological plausibility); a reasonable quantity of food and pattern of consumption required to obtain the claimed effect could be achieved as part of a balanced diet, and specific study groups on which evidence obtained is representative of the target population for which the claim is intended. There is also the need to prevent consumer confusion as well as protecting the public health. Progress toward achieving health claims for flavonoid rich foods such as tea has been slow in Western countries. For related health claims in the USA, there are health claims approved for fruits and vegetables and cancer; fruits, vegetables and grains containing fiber (especially soluble fiber) and risk of coronary heart disease; and soy protein and risk of coronary heart disease. However letters of denial were sent for proposed health claims on green tea and decreased risk of cardiovascular disease, gastric cancer, colorectal cancer, esophageal, pancreatic and other cancers. For green tea and cancer the FDA concluded that it was highly unlikely that green tea decreased risks of cancers of the breast and prostate. EFSA denied the substantiation for the health claims related to Camellia sinensis (L) Kuntze (tea), including catechins from green tea, and their contribution to the maintenance or achievement of a normal body weight, increased beta oxidation of fatty acids leading to a reduction in body fat mass, and maintenance of normal blood glucose concentrations. I also denied those related to Camellia sinensis (L) Kuntze (tea) and the catechins and improvement of endothelium-dependent vasodilatation, maintenance of normal blood pressure, of normal blood glucose concentrations, of normal blood LDL–cholesterol concentrations, protection of the skin from UV induced (including photo-oxidative) damage, protection of DNA from oxidative damage, protection of lipids from oxidative damage, contribution to normal cognitive function, the cardiovascular system, invigoration of the body, decreasing potentially pathogenic gastrointestinal microorganisms, immune health and the mouth. Also EFSA denied the dossiers on substantiation of health claims related to Camellia sinensis (L) Kuntze (tea), including the catechins in green tea and tannins in black tea, and protection of DNA, proteins and lipids from oxidative damage, reducing of acid production in dental plaque, maintenance of bone, decreasing potentially pathogenic intestinal microorganisms, maintenance of vision, maintenance of normal blood pressure, and maintenance of normal blood cholesterol concentrations. Several claims for cocoa flavanols and protection versus oxidative damage and maintenance of normal blood pressure, and cocoa flavonoids and healthy blood flow (endothelium dependent vasodilation which contributes to healthy blood flow) were also not approved. Similarly the EFSA scientific opinion on the substantiation of health claims related to flavonoids and ascorbic acid in fruit juices including berry juices, flavonoids from
citrus, flavonoids from Citrus paradise Macfad, flavonoids, flavonoids in cranberry juice, and polyphenols were not considered to be sufficiently characterized in relation to the claimed effects and that a cause and effect relationship could not be established between the foods/food constituents and the claimed effects. However, interest in developing appropriate claims remains high (Gallagher, Kozianowski, Meijer et al 2012) The opinions of these and other regulatory agencies are worth reading and instructive in suggesting potential improvements in data collection and studies in the future.

Next steps to explore in assessing the effects of dietary flavonoids on health include improving exposure assessment by developing more complete databases for both foods and supplements. More research on the mechanisms of action of flavonoids in foods will strengthen the biological plausibility for effects in risk reduction, and other effects. It is important to determine whether and how flavonoids bind at receptor sites and the messenger effects, whether there exist interactions between flavonoids and between flavonoids and other constituents in mechanisms of action, and if they are important in determining bioavailability and health effects. The influences of genetics and epigenetic differences in response are also a fertile area for research. The influence of food preparation techniques, food matrices and the microbiome on bioavailability and later metabolism of the flavonoids in foods must be explored. Although to date most food flavonoids appear to be safe, additional research is needed, particularly on highly concentrated extracts of them (Schonthal 2011). Better methods for reporting adverse effects also need to be developed as well (Golder and Loke 2012). More high quality clinical studies are needed including those on the effects of flavonoid rich foods on the gut microbiota (Queipo-Ortuno, Boto-Ordonez, Murri et al 2012) Long term epidemiological cohort studies are needed, with improvements needed in the design, reporting and mathematical models of dose-response that are used in these studies (Dwyer, Erdman, Balentine et al under review 2012). The effect sizes from foods or food constituents are probably small, and so great precision is necessary in measuring them to avoid false negative signals. Also, dose-response relationships may not be linear, and so nonlinear models may need to be employed (Ellinger, Eeusch Stehle et al 2012) In conclusion, much progress has been made and hopes are high that in the future with more and better studies the health effects of these fascinating compounds and the foods that contain them will be better elucidated.

References

De Bock M, Derralk JGB Cuttfield WS Polyphenols and glucose homeostasis in humans JAND 2012:808-815


Golder S, Loke YK Failure or success of electronic search strategies to identify adverse effects data J Med Lib Assoc 2012: 100 (2) 130-134


Schonthal AH. Adverse effects of concentrated green tea extracts. Mol Nutr Food Res 2011; 55: 874-885


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