CURRENT RESEARCH ACTIVITIES

The Food Standards Agency’s antioxidants in food programme – a summary*

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Introduction

A growing body of evidence is accumulating, associating diets rich in fruit and vegetables and other plant foods with moderately lower death rates, specifically from cardiovascular disease (CVD) (Ness & Powles, 1997; Law & Morris, 1998; Simopoulos, 2001) and some types of cancer (Department of Health, 1998). Limited evidence also suggests that such diets may also reduce the incidence of diabetes (Ford & Mokdad, 2001), eye conditions such as macular degeneration and cataract (Goldberg et al., 1998), chronic obstructive pulmonary disease (COPD) (Miedema et al.,...
1993) and hypertension (Appel et al., 1997). This adds support to the recommendation to increase fruit and vegetable consumption.

Cardiovascular disease

Randomized primary and secondary intervention trials with antioxidant supplements (vitamin C, vitamin E or β-carotene) have failed to show any consistent benefit on CVD, although the scientific basis and results from observational studies have been convincing. The studies have typically used high doses of a single antioxidant nutrient – results from trials examining the effect of a balanced combination of antioxidants at levels present in foods are anticipated. Although other substances that are antioxidants in their own right (e.g. flavonoids and lycopene) or components of enzymes with antioxidant properties (e.g. selenium) are being promoted to prevent heart disease, there are fewer studies using these substances and to date the results have been even less convincing.

Macular degeneration and cataracts

Although evidence is accumulating to suggest a protective role of fruit and vegetables in the development of age-related macular degeneration and cataracts (Hankinson et al., 1992; Brown et al., 1999; Jacques et al., 2001), to date the results from intervention trials have been inconsistent (Teikari et al., 1997). Therefore, it is not possible to conclude that antioxidants in general or any particular dietary antioxidants have a specific role in the prevention of these conditions.

Diabetes

Enhanced oxidative stress may occur with diabetes (Tsai et al., 1994; Reaven, 1995), suggesting a potential benefit from increased antioxidant intake. Intervention studies, however, have not demonstrated any conclusive benefits from antioxidant supplementation (National Academy of Sciences Food and Nutrition Board, 2000).

Cancer

Fruit and vegetables have been shown to be protective against the risk of developing cancer. Additionally, observational studies, generally, have found an inverse association between intake of antioxidant nutrients (which are a good indicator of fruit and vegetable intakes) and cancer risk. The hypothesis that supplementation of antioxidant nutrients can reduce the incidence of cancer has not generally been supported by randomized trials (Greenberg et al., 1990; ATBC, 1994; Hennekens et al., 1996; Rautalahti et al., 1999; Albanes et al., 2000; Virtamo et al., 2000). Additionally, some trials have even suggested possible harm in certain subgroups, e.g. current smokers or previous heavy smokers (Ommen et al., 1996; ATBC, 1994; Rautalahti et al., 1999; Albanes et al., 2000; Virtamo et al., 2000).

Chronic obstructive pulmonary disease

High doses of vitamin C (500–1000 mg day⁻¹) may prevent the development of COPD, including asthma and bronchitis (Schwartz & Weiss, 1994; Hatch, 1995; Forastiere et al., 2000) or help to relieve some symptoms (Hatch, 1995; Cohen et al., 1997). The high amount needed suggests the mechanism of these effects may not be due to the antioxidant action of the vitamin.

Summary of the antioxidants in food research programme

The Food Standards Agency (FSA) and previously the Ministry of Agriculture, Fisheries and Food (MAFF) have funded research into antioxidants in foods since 1991. The overall aim of the Antioxidants in Food research programme was to test the ‘antioxidant hypothesis’ (which proposes that vitamin C, vitamin E, carotenoids and other antioxidant nutrients afford protection against chronic diseases by decreasing oxidative damage) and, if supported, provide information to help define optimal levels of intake of antioxidants in the UK diet.

In June 2001, the British Nutrition Foundation (BNF) began to evaluate 52 research projects funded by MAFF and FSA as part of the Antioxidants in Food programme. These projects
addressed biomarkers of oxidative damage, supplementation \textit{(in vitro} and human studies) and bioavailability of antioxidants and effects on gene expression. The BNF's objectives for the evaluation were:

1. to provide a critical overview of the research commissioned in the programme and to place this in the context of the international research effort in the field;
2. to consolidate the findings from the different research projects and evaluate each of the biomarkers studied under the programme;
3. to address whether or not the evidence available supported the ‘antioxidant hypothesis’; and
4. to provide a critical evaluation of the programme to date, in particular assessing whether the programme provided a robust scientific case to proceed to a sufficiently powered multicentre intervention study.

\textbf{Methods}

The evaluation process included consultation with an international Steering Group, most of which was by e-mail or telephone. Towards the end of the project, however, the Steering Group met at a workshop, to discuss results from past projects, the current unanswered questions and the best way forward for future work.

The research programme mainly focused on development of biomarkers of oxidative damage that might be suitable for use in intervention trials in human subjects, as measures of the effect of dietary change. It had not attempted, in a systematic way, to understand the mechanisms that involve antioxidants and which are associated with chronic diseases such as CVD and cancer. Instead, the assumption had been that if antioxidants can be shown to reduce oxidative damage, a beneficial effect on disease risk was more likely.

Also included within the programme were projects that focused on the bioavailability of antioxidant substances and effects on gene expression. A number of projects also included small human intervention studies, the primary purpose of which was to test the validity of biomarkers developed or refined within the programme.

The findings of the evaluation were considered in the context of other, recently completed and on-going reviews, which included:

1. The USA’s National Academy of Sciences review of vitamin C, vitamin E, selenium and carotenoids (National Academy of Sciences Food and Nutrition Board, 2000);
2. the EU-funded EUROFEDA project (Lindsay & Astley, 2002);
3. the EU-funded ESCODD project (http://www.rowett.ac.uk/escodd);
4. the work of the FSA’s Expert Group of vitamins and minerals (http://www.food.gov.uk); and
5. the review conducted by BNF of the FSA’s \textit{Optimal Nutrition Status} research programme (Buttriss & Hughes, 2000; Buttriss \textit{et al.}, 2000; Hughes & Buttriss, 2000a; b; British Nutrition Foundation, 2001; Buttriss & Hughes, 2002).

\textbf{Results}

Following the evaluation, a number of recommendations were made to the FSA, including:

1. It would not be appropriate to begin a multicentre intervention trial at this point in time.
2. The FSA Research programme should be refocused to consider a wider range of potential mechanisms of action, not just prevention of oxidative damage, with the ultimate aim of improving understanding of whether or not the link between plant food consumption and reduced chronic disease risk is causative, by identifying mechanisms of action for substances within the foods.
3. More emphasis should be placed on studying the bioavailability (absorption, metabolism and turnover, tissue and cellular distribution) of a range of plant-derived substances, including polyphenols (e.g. the flavonoid subclasses) as well as recognized vitamins and minerals, to establish whether \textit{in vitro} effects are applicable to the \textit{in vivo} situation.
4. More emphasis should also be directed to understanding the functions of plant-derived nutrients and other bioactive substances at a tissue and cellular level, and the impact on these (and on bioavailability) of factors such as genotype, age and ill health. A starting point could be a review of
the published literature to establish currently available information about a range of key components of plant foods, e.g. certain nutrients and classes of polyphenols, including interaction between them, dose–response relationships, and groups of the population more likely to have low intakes of these.

5 Human studies should involve subject groups in whom a response might be anticipated, e.g. those with low plasma levels of the substance of interest.

6 There is a need for further collaborative studies (perhaps involving EU funding), such as the ESCODD study (which focused on DNA oxidation), which compare and validate different methods of measurement of biomarkers. In addition, the EU-funded EUROFEDA study may also provide useful information to aid decision making.

7 In parallel with this, work is needed on the factors that influence successful modification of food selection. There is also an important role for product innovation, particularly in relation to vegetables.

Discussion

To date much attention has focused on the potential for prevention by antioxidants of oxidative damage to DNA, in particular, but also to proteins and lipids. This damage is caused by interaction with oxygen or nitrogen free radicals (Buttriss et al., 2002a, b) and is thought to be associated with mutations to DNA which, if not repaired, could lead to cancer. Similarly, damage to lipids and lipoproteins has been linked with atherosclerosis. Oxidative damage to these molecules is now recognized as a process that occurs routinely in cells, as well as being associated with disease and ageing processes. Little is yet known about what might be regarded as a normal level of endogenous oxidative damage or what level might signify increased risk of disease. Furthermore, it has often been taken for granted that generation of oxygen and nitrogen free radicals is a detrimental event that should be prevented, but it is now recognized that reactive oxygen and nitrogen species are important in defence against infection, act as signalling molecules in cells and may also be important in triggering events such as apoptosis (programmed cell death). In this context, there is the potential for the requirements of antioxidant molecules within cells to be very closely linked with critical functions such as signal pathways and gene expression, disruption of which could be detrimental to cell functioning and survival.

From evaluating the projects in this programme, it became apparent that in future the focus should not solely be on antioxidant mechanisms as other nonantioxidant-related mechanisms may be responsible, at least in part, for the positive benefits observed. It is also clear that interest in measurement of oxidative damage and the impact of this on antioxidants has run ahead of the basic and necessary underpinning research on the functional effects of antioxidants, their bioavailability and their tissue distribution. This applies in particular to plant bioactive substances such as the flavonoid substances and carotenoids.

A major objective of the evaluation was to establish whether or not there was sufficient, robust scientific evidence to justify funding a multicentre intervention trial. It was the BNF’s view (and that of the Steering Group) that, currently, too many unanswered questions remain to progress to this stage, e.g. the extent of knowledge of the bioavailability of many substances is still very limited.

Nevertheless, there is ample scope for a refo-cused programme of work that concentrates on establishing the functional effects and bioavailability of various plant food components, including the so-called antioxidant nutrients, but which takes a broader view on mechanisms of action, e.g. the interactions between dietary factors and the immune system, markers of endothelial damage, modulation of phase I and II enzymes, and the effects on gene expression and cell signalling.

Knowledge about the bioavailability of many of the substances of interest is still very limited. Little is known about the proportion of some dietary compounds of interest that reach the tissues; why some substances are actively concentrated in certain parts of the body (e.g. the carotenoids lycopene and zeaxanthin are actively concentrated in the prostate gland and macular region of the eye, respectively); whether particular metabolites are important and their fate.
Future studies in humans should focus on groups with low intakes/status of the substances in question and perhaps those people more likely to be susceptible to oxidative damage (e.g. smokers, those with certain polymorphisms, or those with established disease) or those more likely to benefit from an increase in supply of the plant constituents (e.g. because of previous low intake). The programme has been hampered by its focus on healthy nonsmokers and younger people. Future studies should also clarify safety issues, e.g. whether or not some antioxidant nutrients act as pro-oxidants in vivo in some circumstances.

Such an approach should help the Agency to formulate more specific and focused dietary messages, both in terms of population subgroups and in terms of specific food items.

**Conclusion**

The establishment by MAFF of the *Antioxidants in Food* programme was groundbreaking and the research that has arisen from the programme has been very important, as it has focused attention on disease prevention rather than on treatment. The programme has helped to progress the identification of biomarkers, in particular.

It can be concluded that there is associative evidence from observational and intervention studies in humans that a diet rich in plant foods (particularly fruit and vegetables) conveys health benefits, as do high plasma levels of several nutrients found in these foods and known to be antioxidants. However, currently there is no evidence that any particular nutrient or class of bioactive substances makes a special contribution. There is still a lack of understanding of the mechanisms underpinning the apparent protective effect of plant foods and, as yet, there is no clear picture of which components are effective and hence no way of predicting whether all or just some plant foods are important in this respect.

The suggestion that antioxidant supplements can prevent chronic diseases, such as cancer and heart disease, has not been proved or consistently supported by the findings of published intervention trials. The current evidence concerning plant foods and health has been reviewed by a BNF Task Force, the report of which will be published in 2003. In particular the Task Force has focused on plant bioactive substances: flavonoids and allied phenols and polyphenols, terpenoids (e.g. carotenoids and plant sterols), and sulphur-containing compounds (e.g. glucosinates) and alkaloids.

Further evidence is required regarding the efficacy, safety and appropriate dosage of antioxidants in relation to chronic disease. Until such evidence is available, the most prudent public health advice is to increase consumption of plant foods, especially fruit and vegetables (selecting a broad variety of types because their constituent profiles vary). The government has initiated a programme aimed at increasing the fruit intake of school children, the school fruit scheme, and is also developing a five-a-day campaign aimed at the general population. There is scope for many local schemes and projects, and a particular need to encourage vegetable consumption as evaluation of studies in the USA has shown that fruit consumption is more readily increased than vegetable intake (Potter et al., 2000). A summary of projects directed at schoolchildren can be found in a new BNF Briefing Paper, *Schoolchildren, Nutrition and Health* (British Nutrition Foundation, 2002).

**References**


