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Symposium on 'Nutritional supplements and drug efficacy'

Nutritional supplements and conventional medicine; what should the physician know?

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Almost anything that is swallowed in pill or potion form that is not a licensed medicine is, by default, legally classified as a dietary supplement. The present paper is an overview of supplement use and is intended to provide a logical framework for their discussion. Five major supplement categories are identified: essential micronutrients; other metabolites that have vitamin-like roles; natural oils; natural plant or animal extracts; antioxidants, which span the other categories. Supplement usage is also classified into broad categories. Examples of each supplement category and usage are briefly discussed. Some potential hazards of supplement use are also outlined; many substances in supplements are either not found in normal UK diets or consumed in much greater amounts than would be found in food. Many supplements are used for pharmaceutical purposes and sold as supplements to avoid the expense of acquiring a medicinal licence and to avoid the stricter quality-control regulations that apply to medicines. The use of supplements to ensure nutritional adequacy and as possible conditionally-essential nutrients is briefly discussed, as is their essentially pharmaceutical use for the prevention and alleviation of disease. There is critical discussion of whether the use of antioxidant supplements is justified or even if it is reasonable to promote a particular food on the basis of antioxidant content alone. Much of the research on supplements is reductionist, commercially sponsored or has other weaknesses; so, despite decades of use and research there is still uncertainty about their efficacy in many cases.

Dietary supplements: Micronutrient deficiencies: Antioxidants: Conditionally-essential nutrients

Supplements are often taken for pharmaceutical rather than nutritional reasons, i.e. to prevent or treat disease, but they are sold as dietary supplements to avoid the need to demonstrate their safety and efficacy to the UK Medicines and Healthcare Products Regulatory Authority. A dietary supplement is subject to food laws and so it is not permitted to make any medicinal claims relating to treatment or prevention of specific diseases, but more general health claims, e.g. 'helps to maintain a healthy heart' or 'helps to maintain healthy joints', can be made. In practice, medicinal claims can be brought to the attention of the supplement-buying public, and supplements can also be obtained from suppliers who are outside of British and EU jurisdiction, e.g. from the Channel Islands.

Before a medicinal licence is granted the safety and efficacy of the product must be demonstrated. Dietary supplements are permitted unless there is evidence of harm. A supplement may continue to be sold despite evidence that it is ineffective and possibly even when there is evidence of negative long-term effects.

Several all-embracing definitions of dietary supplements have been made[1]. Rather than another definition, five categories have been identified into which most supplements fit:

1. single or combined vitamins and minerals;
2. organic compounds that are normal body metabolites but not recognised as essential nutrients because they are synthesised endogenously, e.g. glucosamine, S-adenosylmethionine, L-carnitine and ubiquinone 10;
3. natural extracts that may contain bioactive substances (e.g. garlic (*Allium sativum* L.), soyabean, *Ginkgo biloba* L., ginseng (*Panax* spp.));

Abbreviation: RNI, reference nutrient intake.
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4. natural fats and oils such as fish oil and evening primrose (*Oenothera biennis* L.) oil;
5. antioxidants, which span the other categories listed[2]; thus, vitamin E, β-carotene, lycopene, Se, ubiquinone 10 and extracts of green tea and milk thistle (*Silybum marianum* (L.) Gaertner) are all marketed as antioxidants.

Uses of supplements

Supplements are taken for many specific purposes, but most are covered by four broad headings: (1) to ensure micronutrient adequacy; (2) to compensate for some (perceived) increase in need or defective handling of a nutrient or metabolite; (3) to prevent or treat illness; either to alleviate or reverse existing conditions or to reduce the long-term risk of developing a chronic disease; (4) to improve athletic performance.

Possible adverse consequences of supplement use

Supplements may have toxic effects *per se*; this risk will increase with dose and duration of use.

> *'All substances are poisonous; there is none which is not a poison. The right dose differentiates a poison and a remedy*' Paracelsus 1493–1541

Even essential nutrients such as retinol and cholecalciferol have toxic and potentially-fatal effects at high doses. Fe poisoning is one of the most common causes of accidental poisoning in children.

If a micronutrient supplement is taken in order to ensure nutritional adequacy then the dose is likely to be based on the RDA and comparable with the amounts consumed in a normal diet. When supplements are taken for pharmaceutical purposes then pharmacological doses may be taken for extended periods. Cod liver oil supplements have traditionally been used to ensure vitamin A and D adequacy, but when taken to boost intakes of long-chain *n*-3 PUFA these fat-soluble vitamins may now reduce the amount of oil that can be taken without risking vitamin overdose. Many substances in natural extracts are not normal dietary constituents.

Even if a substance sold as a supplement is not harmful *per se*, because of poor quality control it may be contaminated with other harmful substances such as heavy metals. Synthetic drugs have been surreptitiously added to some supplements, particularly ethnic medicines[3]. There is no guarantee of their identity, purity, strength and bioavailability, and a high proportion of supplements sold in the USA fail on one or more of these criteria. Of thirty-five multinutrient preparations eleven were found to fail on these criteria, including one aimed at children that contained excessive amounts of vitamin A and one for women that was contaminated with Pb[4] (part of the extensive testing performed by ConsumerLab (www.consumerlab.com), an independent testing organisation that performs testing of supplements on the American market). Natural extracts pose particular problems because the 'active' ingredient is often uncertain and even when standardised they may not contain the claimed amount of 'active' ingredient. Samples of St John's wort (*Hypericum perforatum*) tablets purchased in London were found to contain between one-third and two-thirds of the stated hypericin content, and hypericin is probably not the 'active' compound, i.e. these extracts were probably standardised to the wrong ingredient and contained less than the claimed content of this ingredient[5]. Preparations of *Spirulina geitleri* have been marketed as a source of vitamin B_{12} suitable for vegans, but the vitamin B_{12}-like compound found in this alga is not biologically active in mammals[6].

Supplements can be used as an easy alternative to making more difficult and more useful changes in diet and lifestyle. Individuals may take an antioxidant supplement to 'soak up' the extra free radicals generated by exposure to cigarette smoke or take milk thistle to protect their liver from alcohol abuse or take plant extracts rather than eat five portions of fruit and vegetables daily.

Substances in supplements may interact with prescribed medicines and either reduce their effectiveness or even increase their potency. For example, in March 2000 the UK Department of Health issued a warning that St John's wort extracts may reduce the effectiveness of several prescription drugs and may increase the effects of commonly-prescribed antidepressants[7].

Supplements may be an expensive way of obtaining common food components; use of multiple supplements may divert money from more useful purposes such as food or heating. They tend to introduce a medical perspective to eating and undermine its social, cultural and pleasurable aspects.

Vitamins and minerals

Micronutrient adequacy in the UK

Micronutrient supplements are often dismissed as a waste of money because micronutrient deficiencies rarely occur in healthy affluent populations and because supplements are usually taken by those who need them least. Supplement use certainly is concentrated in those with the highest nutrient intakes from food[8,9] and declines with declining social class[10]. However, surveys of British adults[8], schoolchildren[11] and elderly adults[12] all suggest that any assumption of general micronutrient adequacy in the UK may be too complacent. Table 1 shows an analysis of the vitamin adequacy of British adults[13]. Average intakes of the whole sample seem reassuring because they are all above the reference nutrient intake (RNI) and usually well above it. Average intakes are lower in the youngest age-group (19–24 years) and the average vitamin A intake of this group is well below the RNI. Table 1 also shows that substantial numbers of adults have recorded vitamin intakes below the lower RNI or have biochemical indications of unsatisfactory status (1% of British adults represent >250 000 individuals). The lower RNI is theoretically sufficient for 2·5% of the population, but low intakes will not be restricted to those with low requirements. Other examples of unsatisfactory micronutrient intakes or biochemical status in British adults and children are listed in Table 2.

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Table 1. The vitamin adequacy of adult British diets aged 19–64 years[13]

	Average intake (% RNI)				Percentage below LRNI				Percentage below biochemical threshold			
	Men		Women		Men		Women		Men		Women	
Age-group (years).....	19–64	19–24	19–64	19–24	19–64	19–24	19–64	19–24	19–64	19–24	19–64	19–24
Vitamin A (retinol equivalents)	130	80	112	78	7	16	9	19	0	0	0	0
Thiamin	214	160	193	181	1	2	1	0	3	0	1	0
Riboflavin	162	129	146	126	3	8	8	15	66	82	66	77
Niacin equivalents	268	232	257	246	0	0	1	2				
Vitamin B_6	204	189	169	165	1	0	2	5	10	4	11	12
Vitamin B_{12}	431	296	319	266	0	1	1	1	2	0	4	5
Folate*	172	151	125	114	0	2	2	3	4	13	5	8
Vitamin C	209	162	202	170	0	0	0	1	5	7	3	4
Vitamin D† (μg)	3·7	2·9	2·8	2·3	–	–	–	–	14	24	15	28

RNI, reference nutrient intake; LRNI, lower RNI.
*Biochemical value is erythrocyte folate indicating marginal status.
†No adult RNI or LRNI for vitamin D; absolute values given.

Table 2. Some further examples of apparently unsatisfactory micronutrient intakes or biochemical status in the British population[11–13]

25% of women (19–64 years) had recorded Fe intakes below the LRNI and 11% had serum ferritin levels indicative of low Fe stores (corresponding values in those aged 19–24 years were 42% and 16% respectively)
8% of women aged 19–24 years had recorded Ca intakes below the LRNI
Approximately 20% of adolescent girls and 12% of boys had recorded vitamin A intakes below the LRNI
Biochemical evidence of poor vitamin D status was found in 13% of 11–18 year olds with higher numbers in the winter months
50% of older girls had Fe intakes below the LRNI appropriate for starting menstruation and 27% had serum ferritin levels indicative of low Fe stores
One-fifth of older girls had riboflavin intakes below the LRNI
Approximately 10% of elderly adults had serum ferritin levels indicative of low Fe stores
8% of free-living elderly adults and 37% of those living in institutions had biochemical evidence of poor vitamin D status
30–40% of elderly adults had low biochemical status for folate
14% of the independent elderly and 40% of the institutionalised elderly had biochemical evidence of poor vitamin C status
High proportions of adults, children and elderly adults had recorded intakes of one or more of the minerals not already listed that were below the LRNI

LRNI, lower reference nutrient intake.

The assumption that unsatisfactory micronutrient intakes are confined to those with unusual dietary choices or special social or medical problems may be too optimistic. Falling energy intakes and high consumption of low-nutrient-density foods increase the risk of micronutrient inadequacies. Dietary improvements and increased energy expenditure encouraged by effective health-promotion programmes would be the ideal solution to this problem. However, properly targeted use of moderate micronutrient supplements could be a useful, if not ideal, short-term adjunct to dietary improvement.

Other 'uses' of vitamin and mineral supplements

Micronutrients may be taken for other reasons at doses of several multiples of the RNI or RDA: (1) vitamin C is widely taken in doses of ten to 100 times the RNI in the hope that it will prevent colds and flu. A meta-analysis of twenty-nine trials found no evidence of a preventative effect or benefits of large doses taken at the onset of cold symptoms[14]; (2) vitamin B_6 has been widely taken by women to alleviate premenstrual symptoms. Doses of ≤100 mg/d may be used compared with average UK intakes of 2 mg/d. A safe upper limit of 10 mg/d has been suggested because of evidence from animal studies that higher doses may be neurotoxic[15].

Very large supplements (20 × RNI) of folic acid taken before conception and in early pregnancy greatly reduce the recurrence of neural-tube defects in women with a previously-affected pregnancy[16]. More modest doses reduce the rate of first occurrence of neural-tube defects[17]. Extra folic acid may ameliorate the effects of a genetic variation in a folate-dependent enzyme that predisposes to neural-tube defects[18]. All sexually-active fertile British women are advised to take folic acid supplements (2 × RNI) and advice to take peri-conceptual folic acid supplements dates back to 1992[19].

In 2000 a UK expert group[20] recommended that flour should be fortified with 2400 μg folic acid/kg, but this recommendation has not yet been implemented. Campaigns to encourage the use of folic acid supplements have had no measurable impact on the incidence of neural-tube defects even after 6 years duration, but rates have fallen sharply and immediately after the introduction of food fortification in the USA, Canada and Chile[21]. To be maximally effective extra folic acid needs to be taken in the peri-conceptual period, particularly by those with the lowest dietary intakes; ideally, supplementation should

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start before conception. Yet, half pregnancies are unplanned and supplements are generally taken by those with highest dietary intakes. This situation may indicate a general weakness of any health-promotion strategy that relies on the use of supplements.

Fortification in the UK has been delayed by safety concerns, particularly that extra folic acid might mask the haematological manifestations of vitamin B_{12} deficiency in elderly adults and thus delay diagnosis until permanent neurological damage has occurred. A safe upper limit of 1·5 mg folic acid/d has been suggested[15], which compares with average folate intakes in the elderly of $<300\,\mu g/d$ and 30–40 % show biochemical evidence of folate deficiency[12]. Folic acid supplements may also lower homocysteine levels in blood, and elevated homocysteine levels are associated with increased risk of heart disease[22]. Has justifiable caution about a fortification programme aimed at benefiting a small minority become indecision?

Metabolites other than vitamins

Many dietary supplements are natural metabolites that have vitamin-like biochemical functions, such as being enzyme cofactors or precursors for the synthesis of other biologically-important molecules.

These metabolites are not 'essential' because they are synthesised endogenously. Their use as supplements implies that endogenous synthesis is sometimes suboptimal, e.g. insufficient in pathological states or for optimal health or athletic performance. L-3,4-Dihydroxyphenylalanine used to treat Parkinson's disease is a good example of a natural metabolite with proven therapeutic value.

The distinction between essential and non-essential nutrients is not absolute. Some nutrients are termed conditionally essential and 'must be supplied exogenously to specific populations that do not synthesise them in adequate amounts'[23]. These substances are only essential in certain pathological states, in newborn infants or in individuals with certain inborn errors of metabolism. Certain genetic defects of fatty acid metabolism or carnitine transport make carnitine an essential nutrient. The amino acids cysteine and tyrosine are essential for premature babies because the synthetic enzymes develop in late gestation and they may become essential in liver cirrhosis. Even some vitamins are only essential under some conditions, e.g. vitamin D only when there is inadequate exposure to sunlight and niacin only if supplies of tryptophan are limited. Deficiency syndromes are rarely seen for some vitamins like biotin and pantothenic acid.

Glucosamine is produced endogenously by amination of glucose and is manufactured for supplements by acid-hydrolysis of shellfish shells. Glucosamine is a major constituent of the polysaccharide components of proteoglycans in cartilage. If endogenous production of glucosamine is rate limiting in the production of proteoglycans then supplements of glucosamine might accelerate proteoglycan production and reduce cartilage erosion and accelerate repair in arthritic joints. At relatively high concentrations glucosamine has been shown to increase the rate of proteoglycan production in cultured chondrocytes[24]. Evidence from clinical trials does suggest that long-term treatment with glucosamine gives more symptomatic relief than a placebo and reduces narrowing of joint space[25]. At the end of a debate in London rheumatologists were evenly split on whether the use of glucosamine supplements for osteoarthritis of the knee was justified[26].

Creatine phosphate is a short-term energy store in muscles that can directly re-phosphorylate ATP. Creatine can be synthesised from other amino acids in the kidney and liver. A typical omnivorous diet contains about 2 g creatine/d from meat and fish. A vegetarian diet contains almost none, but endogenous synthesis maintains the body pool at a normal 120–160 g for adults. Creatine supplements can increase the concentration of creatine phosphate in muscle, which might be useful in boosting anaerobic energy availability during short bursts of intense activity such as sprinting[27].

L-Carnitine is synthesised by trimethylation of the N in the side chain of the amino acid lysine whilst it is linked to other amino acids by peptide bonds. Dietary meat and fish contain carnitine but vegans who have no dietary supply synthesise an estimated 14 mg/d in a 70 kg adult. L-Carnitine is essential for the metabolism of long-chain fatty acids ($C_{\geq 16}$) that can only enter the mitochondria as acyl carnitine esters. Carnitine also maintains a pool of free CoA within the cell by acting as a reservoir for excess acyl residues. High rates of production of acetyl-CoA during catabolism would limit the availability of CoA for other metabolic pathways, but the transfer of the acetyl group from acetyl-CoA to L-carnitine maintains a pool of free CoA. A genetic defect in the carnitine transporter, certain disorders of fatty acid metabolism, haemodialysis and anticonvulsant therapy can cause carnitine depletion that responds to pharmacological doses of carnitine. L-Carnitine is added to infant formula and regarded as conditionally essential for (premature) infants[28].

Natural fats and oils

These substances include fish liver oil or fish oil, flaxseed oil, evening primrose oil and starflower (*Borago officinalis*) oil. Most oil supplements are taken either because they are rich in *n*-3 PUFA or because they contain γ-linolenic acid (18 : 3*n*-6). They increase the availability of long-chain *n*-3 PUFA or the availability of dihomo-γ-linolenic acid (20 : 3*n*-6; endogenous production of dihomo-γ-linolenic acid is limited by the availability of γ-linolenic acid). Increased long-chain *n*-3 PUFA increases the proportion of eicosanoids produced from EPA (20 : 5*n*-3) rather than from arachidonic acid (20 : 4*n*-6). γ-Linolenic acid increases the production of eicosanoids from dihomo-γ-linolenic acid. This change in the balance of eicosanoid production may dampen the inflammatory response, reduce platelet aggregation and affect other physiological and pathological processes that are regulated by eicosanoids. Long-chain *n*-3 PUFA, especially DHA (22 : 6*n*-3), are normal components of membranes and the high *n*-6 PUFA : *n*-3 PUFA in many modern diets may limit the availability of DHA for optimal membrane function, particularly in the brain.

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There are many claims for oil supplements, such as: fish (liver) oils reduce the risk of having a heart attack, alleviate the symptoms of arthritis and improve behaviour and concentration in schoolchildren; evening primrose oil and other sources of γ-linolenic acid such as starflower oil reduce symptoms of the premenstrual syndrome, especially mastalgia (breast pain).

Interest in the possible cardio-protective benefits of fish oils was stimulated in 1991 by publication of a trial that suggested that eating two weekly portions of oily fish or taking fish oil capsules leads to reduced total mortality in men in the 2 years after a first heart attack[29]. A major commissioned review of the effects of *n*-3 fatty acids from fish oil or fish on CVD has concluded that: randomised controlled trials of fish oil supplements suggest that they reduce all-cause mortality and cardiovascular events in subjects with existing diagnosed CVD; cohort studies report a reduction in all-cause mortality, cardiovascular deaths and myocardial infarction associated with high fish oil consumption over 10 years[30].

Natural extracts

Many of the natural extracts sold as dietary supplements have a long history of use as folk or herbal remedies and are sold as dietary supplements for commercial convenience. Examples of such 'supplements' used to treat specific medical conditions are: *Agnus castus* for premenstrual syndrome; Saw palmetto (*Serenoa repens*) for benign prostatic hyperplasia; St John's wort for mild depression; Echinacea (*Echinacea purpurea*) to boost the immune system and prevent or treat colds and flu.

Other supplements are extracts of common food substances such as green tea, soyabeans, garlic, bilberries (*Vaccinium myrtillus*) and turmeric (*Curcuma longa*), and therefore have more claim to being 'nutritional' supplements.

Usage is based on belief in the therapeutic benefits of secondary metabolites in the extracts that may serve roles in the plant such as: insect attractants; discouraging consumption by birds, animals or insects; protection from microbial damage; protection from UV radiation.

There are many thousands of secondary metabolites and some are unique to a particular plant or group of plants. They have been classified into four major categories: terpenoids; phenols and polyphenols; alkaloids; S-containing secondary metabolites[31].

Terpenoids

The terpenoids comprise variable numbers of C_5 isoprene units and are derived from isopentyl diphosphate:

$$CH_2{=}CH(CH_3){-}CH_2{-}CH_2{-}O{-}P{-}P.$$

There are over 25 000 terpenoids and they can be subdivided into the hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), triterpenoids (C_{30}), tetraterpenoids (C_{40}) and the higher terpenoids ($C_{>40}$). Several volatile oils that impart a characteristic odour to plants such as coriander (*Coriandrum sativum*), lemon and peppermint (*Mentha* × *piperita)* are monoterpenes. The plant sterols sitosterol and stigmasterol and the saponins are triterpenoids and the carotenoids are tetraterpenoids. Ubiquinone is a higher terpenoid derivative.

Phenols and polyphenols

The phenols and polyphenols have at least one aromatic ring with at least one attached hydroxyl group and they range from simple compounds with a single aromatic ring through stilbenes and flavonoids with two aromatic rings, up to complex polymeric forms and conjugates such as the flavonol glycosides. Examples include: the stilbene *trans*-resveratrol famously found in red wine and produced by the vine to combat microbial attack; flavonols such as quercetin and kaempferol found in tea and red wine; the isoflavones genisten and daidzein, which are phytoestrogens found in soyabeans; complex polymeric flavonols found in chocolate, red wines and black tea.

Alkaloids

The alkaloids are N-containing compounds synthesised from amino acids or purine bases. Many have pharmacological activity, some are potent poisons and a number are used as medicinal drugs. They include theobromine in chocolate, caffeine, atropine, curare, the anti-cancer drug vincristine, cocaine, morphine and quinine.

Sulphur-containing secondary metabolites

S-containing secondary metabolites comprise the glucosinolates found in cruciferous plants such as cabbage, rape (*Brassica napus)*, watercress (*Nasturtium nasturtium-aquaticum* L.), turnip (*Brassica rapa* var. *rapa*) and mustard (*Brassica juncea*) and the S-alkylcysteine sulphoxides found in members of the Allium or onion family that are synthesised from cysteine. The predominant S compound in whole garlic is allylcysteine sulphoxide, which is enzymically converted to allicin when the clove is cut or crushed. Allicin is regarded as the active ingredient in garlic supplements; it is an unstable compound and is destroyed during cooking:

$$CH_2{=}CH{-}CH_2{-}S{-}S{-}CH_2{-}CH{=}CH_2.$$

Use of natural extracts

Natural extracts can undoubtedly have powerful therapeutic properties because they are the origin of many medicinal drugs such as: several of the alkaloids listed earlier; aspirin, which is derived from salicylic acid found in willow (*Salix* spp.) bark; digoxin derived from the purple foxglove (*Digitalis purpurea*). The assumption that 'natural' equates with safer is not consistent with the potent poisons also found in natural extracts.

Garlic

Garlic supplements are taken in the belief that they will lower plasma cholesterol levels. A major commissioned

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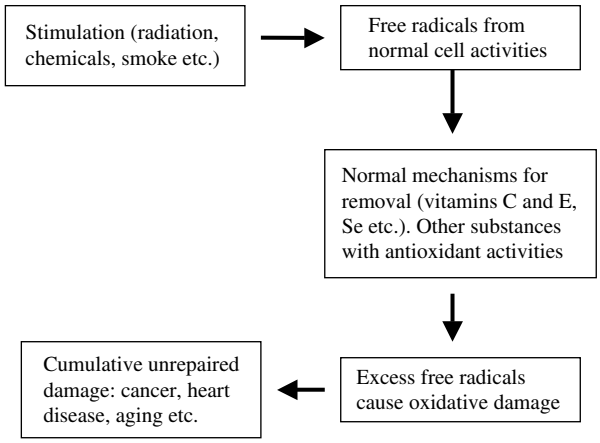

Fig. 1. The free radical theory of disease.

review of the effects of garlic supplements has found that thirty-seven high-quality trials consistently report a small but significant reduction in total plasma cholesterol after 1 month and 3 months but not in those eight trials that continued to 6 months. These results suggest that any effect of garlic on blood cholesterol is small and clinically insignificant and may well be only transient[32].

Phyto-oestrogens

The phyto-oestrogens present in soyabean extracts have very weak oestrogenic activity and are termed partial agonists. In post-menopausal women with little endogenous oestrogen production they may boost overall oestrogen response, but paradoxically may reduce overall oestrogen effects in younger women by competing for receptors with more-potent endogenous oestrogen. They are marketed as a 'natural' alternative to pharmaceutical oestrogen replacement in older women to alleviate acute menopausal symptoms and to reduce bone loss and osteoporosis. In younger women it is claimed that they may reduce breast-cancer risks by modulating the effects of endogenous oestrogen[33].

Antioxidants

Free radicals are very reactive chemical entities that are produced as by-products of normal oxidative processes in cells. They can react with and cause oxidative damage to cellular components such as proteins, DNA, PUFA residues and complex carbohydrates. Many noxious stimuli such as ionising radiation, cigarette smoke, sunlight or toxic chemicals may increase free radical generation. The cumulative damage caused to cellular components by free radicals can lead to chronic degenerative changes and to diseases such as cancer and atherosclerosis. Cellular antioxidant mechanisms quench free radicals and repair the damage they cause but unrepaired damage by free radicals leads to chronic disease (see Fig. 1). Essential nutrients such as vitamins E and C, Se and Zn have established roles in these antioxidant mechanisms. Many other substances found in food and supplements also have antioxidant activity, e.g. the carotenoids in coloured fruits and vegetables and the polyphenols found in foods such as red wine, tea, nuts, many fruits and even chocolate. There are frequent media reports suggesting that a particular food or supplement can prevent cancer or chronic disease. These claims are often based on little more than chemical detection of an antioxidant or experimental evidence that very high intakes of the food or supplement can reduce some short-term measure of oxidative stress in animals, volunteers or *in vitro*.

Evidence of holistic benefit from the consumption of antioxidant supplements is sparse. The so-called 'ACE vitamins' (vitamins A, C and E) are amongst the most thoroughly tested of the antioxidants. The vitamin A component is usually present as β-carotene because of its low acute toxicity. The antioxidant activity of β-carotene and other carotenoids is unrelated to their vitamin A activity. Several expert groups have concluded that diets rich in fruits and vegetables protect against chronic diseases[34,35] and these are major dietary sources of antioxidants. Observational evidence also suggests that high intakes of β-carotene, vitamin C and/or vitamin E are associated with reduced risk of cancer and heart disease[36–40]. Such observational evidence suggests that supplements of antioxidant vitamins might help to prevent cancer and heart disease.

In contrast to the observational evidence, several large placebo-controlled trials have suggested that supplements of β-carotene are at best ineffective[41] or even positively harmful, especially in smokers who show increased total and cancer mortality[42–44]. Ironically, smokers were chosen as subjects because they were expected to gain most from increased antioxidant intakes. Two major commissioned reports on the effects of antioxidant supplements in the prevention of CVD[45] and cancer[46] have concluded, after reviewing hundreds of clinical trials, that: (1) there is no evidence that vitamin E or vitamin C supplements have any benefit on cardiovascular or all-cause mortality; (2) there in no evidence that vitamin E or vitamin C supplements have any beneficial effect on the incidence of myocardial infarction or have any significant effect on plasma lipids; (3) there is no evidence to support any beneficial effects of vitamins C and/or E in the prevention of new tumours, the development of colonic polyps or in the treatment of patients with advanced cancer.

A meta-analysis of seven large controlled trials of vitamin E supplements has found no evidence of benefits from vitamin E supplements on all-cause, heart disease or stroke mortality. An analysis of eight β-carotene trials has suggested a small but significant increase in all-cause mortality and cardiovascular deaths in those receiving β-carotene supplements of 15–50 mg/d[47]. In 1998 an expert group advised against the use of concentrated β-carotene supplements[35]. A safe maximum dose of β-carotene in supplements of 7 mg/d has been suggested[15], yet tablets containing 15 mg are still on sale.

A recent highly-publicised meta-analysis has even suggested that not only β-carotene supplements but also retinol and vitamin E supplements may increase mortality[48]. Furthermore, no evidence was found to support any beneficial effects of β-carotene, retinol, vitamin E,

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vitamin C or Se (either singly or in combination) on mortality risk in primary and secondary prevention trials. A controlled trial of large doses of vitamins C and E for the prevention of pre-eclampsia in women with previous history of this condition has found that it does not prevent pre-eclampsia but does increase the rate of low-birth-weight babies, and there was some suggestion that the onset of pre-eclampsia occurred slightly earlier in the antioxidant group[49].

Neutrophils are assumed to kill ingested micro-organisms by generating an oxidative pulse of free radicals. This assumption encourages a belief in the destructive power of free radicals. It has been suggested that it is protease enzymes produced by leucocytes, rather than free radicals, that kill ingested microbes, and thus that the potential toxic effects of free radicals on human cells may have been overestimated[50].

These studies with the 'ACE vitamins' suggest that it would be unwise to assume that a food or supplement is beneficial just because it has a high chemical content of antioxidants or reduces acute measures of oxidant stress. It cannot be assumed that concentrated antioxidant supplements are invariably safe.

Research on supplements

Many dietary supplements have been on sale for decades and have been the subject of hundreds of research papers, yet it is still difficult in many (most) cases to come to a firm conclusion about the validity of claims made for them. There may be two factors that help to explain this situation.

If a compound shows promise of providing large and immediate therapeutic benefits then it is likely to be recognised and developed by the pharmaceutical industry or orthodox medicine. Many of those that remain are thus likely to be ineffective or have relatively small or delayed benefits that are difficult to demonstrate conclusively.

Much of the research on supplements, and so-called 'superfoods', is reductionist; measuring levels of potentially-bioactive materials, measuring *in vitro* effects or measuring the effects on some acute risk marker. When clinical trials are performed they are often flawed, e.g. small, of short duration, incompletely double-blinded or not properly randomised. When reading through systematic reviews of supplement trials authors almost inevitably comment about the low quality and size of many of the trials, and many trials fail to meet the quality criteria for inclusion in a meta-analysis[2]. The conclusions often change substantially when a meta-analysis is re-calculated using only studies identified as being of the highest quality[25,48]. Much of the research on supplements and on the health benefits of individual 'superfoods' seems geared more towards attracting media attention and gaining a commercial advantage for the research sponsor than finding scientific truth.

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