

# Recommended dietary intake levels for phytochemicals: Feasible or fanciful?

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Phytochemicals are biologically active compounds, found in plants in small amounts, which are not established nutrients but which nevertheless seem to contribute significantly to protection against degenerative disease. At present, most interest in phytochemicals is focused on the polyphenolic flavonoids and on the carotenoids, although allium compounds, glucosinolates, indoles and coumarins have also received attention, especially with respect to cancer. Mechanistically, phytochemicals are thought to act in many ways, which include their activity as anti-oxidants, antibacterial/viral agents, phytoestrogens and as inducers or inhibitors of a variety of key enzymes. Recommended dietary intakes (RDI) are the levels of intakes of essential nutrients considered adequate to meet the known nutritional needs of practically all healthy persons. To be regarded as an essential nutrient, a dietary component must be a single identified compound or a close derivative. It should have a demonstrated key biological role and characteristic deficiency syndrome, both of which should respond to nutritional manipulation and are used as a basis for setting an RDI. In these terms, allocating RDI to phytochemicals is problematic, due in part to the large number of chemically different phytochemicals and the lack of a distinctive deficiency syndrome or inherent physiological role in almost all cases. Accordingly, allocation of a single RDI to a general class of phytochemicals would be impracticable, although for an individual phytochemical it may be feasible if acceptable justification for an RDI is extended to include optimum health and evidence is forthcoming of a key inherent role for that compound in maintaining optimum physiological function. However, a distinction will need to be drawn between phytochemicals that participate as integral components of an essential biological system and become recognized as nutrients and those that act as valuable non-nutrient health-promoting agents. Both classes of phytochemicals occur in foods and both could be incorporated into functional foods. Both could be addressed in recommendations such as dietary guidelines, but at present only established nutrient phytochemicals would be eligible for an RDI.

**Key words:** recommended dietary intakes, dietary guidelines, phytochemicals.

## Introduction

Currently, intense interest is focused on phytochemicals in foods with respect to their potential role in maintaining optimal health and reducing the risk of developing a number of degenerative diseases associated with ageing. As more is learnt about the nature of phytochemicals and the possible mechanisms by which they may operate, the question has been raised whether the point has now been reached where at least some phytochemicals should be accorded a recommended dietary intake (RDI) or a reference value (RV). However, allocation of a RDI or RV to a nutrient requires that they meet certain generally accepted criteria, against which new candidate compounds may be judged. Current evidence with respect to these criteria and phytochemicals suggest that a RDI for phytochemicals as a group, or for individual phytochemicals would not appear to be feasible at this point.

## Phytochemicals

Phytochemicals are biologically active compounds found in plants in small amounts. They are not established nutrients but, nevertheless, seem to contribute significantly to protection against degenerative disease. The term does not apply to compounds used in relation to treating an established acute disease, but rather to substances that are protective at low levels against the development of degenerative diseases over a lifetime.<sup>1</sup>

Epidemiological evidence with respect to cancer and cardiovascular disease cogently suggests that phytochemicals may play a significant part in protection against the development of these diseases. This association has been drawn from the strong correlation that exists between a high dietary intake of fruit and vegetables and a reduction in the incidence of these diseases, which has led nutritionists to investigate the components in fruits and vegetables (phytochemicals) that may confer this protection. At present a large number of phytochemicals have been identified in plant foods (Table 1). The phytochemicals have been demonstrated experimentally to influence a variety of physiological and biochemical events that may underlie the aetiology of several degenerative diseases.

Experimental evidence that phytochemicals influence many cellular mechanisms which may optimize health has highlighted the need to identify clearly which effects may be of greater health significance. Table 2 lists some of the mechanisms determined experimentally for a number of phytochemicals through which they may act to promote optimum health.

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**Table 1.** Foods and phytochemicals possibly involved in optimizing health and protection against disease

Food	Putative phytochemical
<i>Allium</i> sp. (onions, garlic, etc.)	Thioallyl compounds
<i>Cruciferus</i> sp. (cabbage, broccoli, etc.)	Indoles, isothiocyanates
<i>Umbeliferus</i> sp. (carrots, parsnips, etc.)	Carotenoids, terpenes
<i>Citrus</i> sp. (orange, lemon, etc.)	Terpenes, flavonoids
Ginger	Gingerol
Orange/yellow fruits and vegetables	Carotenoids, flavonoids
Tea, wine, cocoa	Catechins, flavonoids

However, a further level of complexity is added to defining the key putative protective mechanism for most phytochemicals because of the many demonstrated effects attributed to them. Table 3 lists several potentially important protective mechanisms for two widely researched phytochemicals, namely the soybean isoflavonoid genistein and the tea flavanoid catechin.

### Recommended dietary intake levels

Recommended dietary intake levels are the levels of intakes of essential nutrients considered adequate to meet the known nutritional needs of practically all healthy persons. Reference values are values which incorporate this principle but are expressed as several different values in order to accommodate a variety of purposes. To be regarded as an essential nutrient and to be allocated a RDI, a dietary component must be: (i) a single identified compound or close derivative; (ii) have a key demonstrable biological role and biochemical mechanism on which the RDI or RV is based; and (iii) exhibit a specific deficiency syndrome or impaired physiological function that has been associated with an inadequate intake of the component and which is responsive to dietary supplementation.<sup>1</sup>

### Issues associated with phytochemical recommended dietary intake levels

Current evidence strongly suggests that phytochemicals may play many key protective roles in the cell, but their specific and unique contribution to this protection is not clear.<sup>4,5</sup> This fact, together with the generally generic effects of phytochemicals on cellular metabolism, makes it difficult to apply the concept of a key identifiable function for a phytochemical on which a RDI can be based. Indeed, compared against the

general criteria used for establishing current RDI levels, several important shortcomings need to be recognized, namely:

1. Potential health benefits are not attributed to a single phytochemical compound. On the contrary, they are associated with foods containing thousands of phytochemicals or with a particular group in which there are often hundreds.
2. The diverse distribution and action of phytochemicals makes it almost impossible to nominate a single key biological role for phytochemicals in general or indeed for individual categories of phytochemicals, or individual compounds.
3. There is no deficiency syndrome or impaired function unequivocally associated with any one or any group of phytochemicals. Rather, the emphasis that has emerged relates to phytochemicals as agents that may promote optimal health on a broad base and reduce the risk of several degenerative diseases.

### Phytochemicals, recommended dietary intake levels and dietary guidelines

In general, most nutritionists recognize the importance of phytochemicals in promoting optimum health, which in turn underlies the dietary emphasis on fruit and vegetables and cereal grains. However, in the present context, the likelihood of one of the new phytochemicals rating a RDI is slender unless:

1. Optimum health *per se* is regarded as an ultimate objective of sufficient importance to be included as a major criterion considered in allocating RDI levels.
2. A specific role is demonstrated for a particular phytochemical in maintaining optimum health, which is not shared non-specifically by other dietary factors.

On the other hand, reference to phytochemicals, both in general and specifically, will probably become more common in dietary guidelines in the future. Indeed, in the recently published *Dietary Guidelines for Older Australians*,<sup>6</sup> specific mention is made in the section discussing vegetables (including legumes) and fruit of the potential health benefits associated with a number of phytochemicals, which includes reference to carotenoids, phytoestrogens, isoflavones, bioflavonoids, isothiocyanates and indole carbinols.<sup>6</sup> The operative distinction is evident — RDI levels are quantitative estimates that require quantitative justification. Dietary guidelines are less quantitative but no less important, and focus more on qualitative issues and lifestyle outcomes. The stage on which phytochemicals will be seen for the next decade will probably occur mainly under the banner of dietary guidelines.

**Table 2.** Putative mechanisms for several phytochemicals possibly involved in protection against degenerative disease<sup>2,3</sup>

Putative mechanism	Phytochemical	Food source
Antioxidant activity	Polyphenols (flavonoids, isoflavonoids) carotenoids	Tea, grape skin, cocoa, green/coloured fruit and vegetables
Altered phase I* and phase II† enzyme activities	Indoles, isothiocyanates, dithiolthiones, polyphenols	Cabbage, brussel sprouts, tea, fruits, cocoa
Weak oestrogenic activity	Isoflavonoids, lignans	Soybeans, flax seed
Anti-inflammatory activity	Thioallyl compounds, catechin, gingerol	Onions, garlic, tea, fruit, ginger
Hypocholesterolemic and antithrombotic activity	Thioallyl compounds, phytoestrogens, flavonoids	Onions, garlic, soybeans, flax seed, tea, cocoa, fruit and vegetables

\*Xenobiotic activating enzymes. †Xenobiotic detoxifying enzymes.

**Table 3.** The multiple actions of phytochemicals

Genistein (Soybean isoflavonoid)	Catechin (Tea polyphenol)
Phytoestrogen	Antioxidant
Inducer	Inducer
Phase II enzymes	Phase II enzymes
Antioxidant	Apoptosis
Inhibitor	Inhibitor
Tyrosine kinase	Carcinogen synthesis
Topoisomerase	Phase I enzymes
Ribosomal S6 kinase	Carcinogen/DNA binding
Cell proliferation	Invasiveness
Angiogenesis	Adhesiveness

### Speculative phytochemical, recommended dietary intake levels and dietary guideline scenarios

#### *A possible phytochemical recommended dietary intake?*

Recognizing the specific and quantitative evidence required for allocation of a RDI, few phytochemicals at present appear to rate serious consideration, although some attention may soon have to be paid to the carotenoids lutein and zeaxanthin on the basis of their putative role in the physiology of the macula or 'yellow spot' on the optic retina. Several reports have recently highlighted the presence of lutein and zeaxanthin specifically in the macula, in precise but different membrane orientations, as well as several oxidized metabolites of these carotenoids.<sup>7-10</sup> The apparent need for these two particular carotenoids to protect the macula against light-induced oxidative injury suggests that they may serve a unique role in reducing the risk of age-related macular degeneration. Should future research substantiate this view, and protection against degenerative disease be accepted as a valid basis for defining an essential nutrient and an accompanying RDI, then these two specific carotenoids with their emerging physiological role may deserve serious consideration for receiving RDI levels.

#### *A less likely phytochemical recommended dietary intake?*

Another class of phytochemicals also currently attracting attention in terms of a possible key physiological role are the catechins in relation to protection against oxidation of low-density lipoproteins (LDL), and an implied reduction in risk of cardiovascular disease. Evidence suggests that early events in atherogenesis might be due to the oxidation of LDL, and that  $\alpha$ -tocopherol may act protectively in this regard to reduce lipid peroxidation.<sup>11</sup> However, effective protection of LDL also requires the presence of other suitable reducing agents or co-antioxidants, without which  $\alpha$ -tocopherol may act as a pro-oxidant. Ubiquinol-10 is the reduced form of coenzyme Q10 and is a powerful lipid-soluble antioxidant which is found in LDL particles and appears to function physiologically as a co-antioxidant together with  $\alpha$ -tocopherol.<sup>12</sup> Experimental evidence also suggests that the presence of several carotenoids in the LDL particle and ascorbate in the plasma may add to the overall co-antioxidant activity.<sup>13,14</sup> Thus, in the presence of aqueous phase oxidizing radicals, ascorbate is consumed first as an antioxidant followed by ubiquinol-10 and, subsequently, by the carotenoids and  $\alpha$ -tocopherol. More recently, other co-antioxidants have been proposed, which include 3-hydroxyanthranilic acid<sup>15</sup> and catechin.<sup>16</sup> These are consumed after ascorbic acid in *in*

*vitro* systems, but before the endogenous lipid soluble LDL antioxidants  $\beta$ -carotene and  $\alpha$ -tocopherol are oxidized. Among the catechins, epigallocatechin gallate (EGCG) exerted the most marked effects.<sup>17</sup> Clearly, if findings in the future confirm a specific role for EGCG in protecting LDL against lipid peroxidation, a cogent case would emerge for EGCG to be considered an essential nutrient with an accompanying RDI. If, however, the role of catechins as LDL anti-oxidants is non-specific and shared by many other water-soluble compounds, then attention will focus rather on the catechins as health-promoting phytochemicals found in certain foods and possibly recommended in dietary guidelines.

#### *A dietary guideline phytochemical*

For several categories of phytochemicals sufficient evidence is probably already available to indicate that they are unlikely to qualify as essential nutrients with RDI levels, but that they are nevertheless valuable dietary factors with significant health-promoting potential.

Typical of this category are the phytoestrogens, which include the fruit flavonoid quercetin, the isoflavonoids genistein and diadzein (which are found in soybeans) and the lignans enterolactone and enterodiol, which are found in oil seeds (particularly flax seed or linseed) and are derived from precursors by bacterial action in the large bowel. Phytoestrogens bind weakly to the oestrogen receptor and, in some cases, may act as anti-oestrogens, thereby reducing the impact of pure oestrogen in hormone-sensitive conditions (e.g., breast cancer). However, in the absence of oestrogen they may be weakly oestrogenic and confer, in part, the benefits of the pure hormone in relation to heart disease, prostate cancer and osteoporosis.<sup>18,19</sup> Clearly, it is highly unlikely that a key inherent physiological role will be demonstrated for phytoestrogens that would justify their inclusion as essential nutrients. Rather it would seem that phytoestrogens may serve a useful role in optimizing health by improving an existing physiological state by a direct mild pharmacological effect. Other phytochemicals in this category may act by the relatively non-specific induction of protective enzymes and thereby maintain biochemical defence systems at near peak levels.

#### **Conclusion**

At present, it seems unlikely that many, if any, phytochemicals will become recognized as essential nutrients in the near future and be accorded RDI levels. On the contrary, they are very much more likely to feature in future dietary guidelines in which their important role in maintaining optimum health will be stressed. The importance of phytochemicals in this regard has been highlighted by Potter and Graves in an evolutionary/adaptational context, which recognizes that the diet to which humans are adapted include regular exposure to substances on which human metabolism is dependent.<sup>20</sup> Reduction in the intake of vegetables and fruit would reduce this exposure and may impair detoxification, antioxidant and other protective functions, and thereby reduce optimum health. A recent, valuable contribution to the phytochemical debate has been made by Wahlqvist *et al.*, who have proposed developing a food-based Index of Preferred Phytochemical Intake (IPPI).<sup>21</sup> Under this proposal,

IPPI foods known to be good sources of a particular class of beneficial phytochemicals are aggregated, thereby providing for optimum intake and synergy, but at the same time avoiding potential toxicity from excessive intakes.

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