Current Therapeutics

Phytochemical Deficiency Disorders:

INADEQUATE INTAKE OF PROTECTIVE FOODS

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Nutrients in foods have historically been classified into macronutrients (protein, carbohydrate, fat, dietary fibre, water and alcohol) and micronutrients (vitamins, minerals and essential elements). Nutritional science has now focused more on the role of specific foods composed of non-nutrient factors, most of which are phytochemicals. These compounds may reduce the risk of chronic non-communicable diseases like cardiovascular disease, osteoporosis, certain cancers, and other health problems like migraine and menopausal symptoms. Phytochemicals may or may not be directly associated with deficiency syndromes, but they do contribute to optimal health.

The Role of Phytochemicals

The human species is quite remarkable among animal species for the way it has established itself globally amongst diverse food supplies. Its biological evolution has not only been advantaged in this way, but is now probably dependent on it for optimal health. Associated with this there has been a social evolution: at first hunting and gathering provided families and small groups with a varied food supply, later subsistence agriculture provided an often narrower and more precarious food supply, affected by weather patterns, pestilence and conflicts. Now it has become evident that, in an urban environment, the food supply needs to reflect a biodiversity which can be difficult to achieve, depending on economic status. Of considerable interest is how new insights into food science are instructing us about the myriad of biologically active compounds in food, especially plant food, known as 'phytochemicals'. These present us with a new era in nutrition science, going beyond nutrient science and linking to our sociocultural roots.

In future, we may prevent or delay the onset of diseases by ensuring adequate dietary intake of non-nutrient factors

The role of specific food phytochemicals in the treatment of health conditions is rapidly unfolding.[1] Phytochemicals may almost be regarded as pharmaceuticals rather than dietary nutrients when they are used to manage clinical conditions. This is not surprising as many important drugs available today were, at least initially, derived from

SALIENT POINTS

- **The term 'phytochemical' covers a large number of non-nutrient factors present in plant foods**
- **Phytochemicals have protective functions that reduce the risk of diseases such as cardiovascular disease, osteoporosis and certain cancers**
- **The key to adequate phytochemical intake is a diet containing a wide variety of unprocessed plant foods, including fruit, vegetables, grains and nuts**
- **There is an increasing tendency to focus on inclusion of beneficial and protective foods in the diet, rather than exclusion of possibly detrimental foods**

plants. An alternative viewpoint is that conditions for which they are used as treatment may have occurred because of inadequate intakes from foods. In future, we may prevent or delay the onset of diseases by ensuring adequate dietary intake of these non-nutrient factors. The emergence of new familial diseases may reflect a change in food culture which has exposed a genetic predisposition.

Definition and History of Phytochemicals

'Phyto' in Greek means plant, thus phytochemicals are 'plant-based chemicals'. Although the term may include all plant chemicals, it is being applied to chemically minor components and ones that have not already been classified as nutrients for humans. Further, the term is not being applied to naturally occurring plant toxicants, although, as with all factors affecting human biology, phytochemicals will have a safety range. These compounds usually exist in plants as secondary metabolites used by the plant for defence and survival. However, they may also appear in animal tissue eaten by humans.

In 1836, Szent-Gyorgyi reported that lemon flavonoids could cure scurvy when vitamin C alone could not. This may have represented functional overlap between the compounds. The term 'vitamin P' was used to define the anti-scurvy activity of some flavonoids which act on the permeability of blood vessels. But when no clear deficiency syndrome could be defined, these flavonoids fell out of scientific favour. They have now reappeared as part of the current interest in phytochemicals.

Dietary fibre serves as a marker for preferred plant foods and the many factors they contain

Until the mid 1980s, the link between coronary heart disease and diet focused exclusively on the lipid hypothesis or the theory that high blood lipids were a significant risk factor in cardiovascular disease morbidity and mortality. A corresponding link has been established between vitamin-rich fruit and vegetables (or the amounts of antioxidant vitamins such as ascorbic acid, tocopherols, retinols and carotenoids that these foods contain) and a decreased risk of death from cancer and cardiovascular disease. The antioxidant effect of vitamin supplements alone, however, is not as potent, and clearly additional benefits or synergism with phytochemicals is found in fresh fruit and vegetables. This is analogous to the apparent benefits of dietary fibre in bowel health, cardiovascular disease, incidence of diabetes and premature mortality, where dietary fibre serves as a dietary marker for preferred plant foods and the many factors they contain.[2]

Classification of Phytochemicals

This may proceed in accordance with plant source, chemistry, or functions. No one classification will be satisfactory because plants will be sources of various chemical and functional classes of compounds, the chemistry is complex and the compounds myriad. What has become clear is that one class of phytochemicals may have several functions, i.e. there are multifunctional compounds. On the other hand, a particular function may be provided by more than one class of phytochemicals. The interaction between the compounds is also likely to be considerable and complex, causing both masking of effects and synergy.

Examples of Phytochemicals

The growing array of phytochemicals opens up opportunities for more healthful food choices and for the development of functional foods to serve particular physiological or pathological needs. Phytochemicals may fall into any one of several categories: carotenoids, flavonoids and isoflavonoids, polyphenols, isothiocyanates, indoles, sulphoraphane, monoterpenes, xanthin and non-digestible oligosaccharides (Table I). Detailed consideration is now given to these categories which are undergoing active investigations for their health properties.

Carotenoids

Carotenoids are natural pigments responsible for many of the brilliant red, orange and yellow colours of edible fruit and vegetables. Some of them are provitamin A while most possess other biological actions, including antioxidant, immuno-enhancement, antimutagenic and anticarcinogenic. Owing to the antioxidant property of carotenoids, the possibility exists that these compounds reduce lipid peroxidation, oxidative stress and free radical damage. Accordingly, they may protect against coronary heart disease, cancer and cataracts.

Flavonoids and Isoflavonoids

Flavonoids are a large group of polyphenolic compounds that occur naturally in vegetables and fruit and in beverages such as tea and wine. They have been studied in relation to decreased vascular fragility. Some flavonoids such as quercetin, kaempferol and myricetin have antimutagenic and anticarcinogenic effects in vitro and in vivo.[3]

It appears that a number of the biological effects of flavonoids may be explained by their antioxidative activity and ability to scavenge free radicals. Quercetin, one of the most abundant natural flavonoids, present in various common vegetables and fruits, has been reported to inhibit oxidation and cytotoxicity of low-density lipoprotein (LDL) in vitro. This property of quercetin, as well as other flavonols, could have important health consequences since oxidised LDL is believed to be atherogenic.

Current Therapeutics

Table I. Phytochemicals and their possible roles in health

Phytochemicals	Some important food sources	Possible roles in health
Carotenoids	Orange pigmented, and green leafy vegetables, e.g. carrots, tomatoes, spinach	Antioxidant Antimutagen Anticarcinogen Immuno-enhancement
Flavonoids, isoflavonoids and saponins	Green and yellow leafy vegetables, e.g. parsley, celery, soy bean and soy products	Antioxidant Anticarcinogen Oestrogenic Immuno-modulating
Polyphenolics	Cranberries, raspberries, blackberries Rosemary, oregano, thyme	Antioxidant Antibacterial Reduce urinary tract infection
Catechins	Green tea	Antimutagen Anticarcinogen Anticariogen
Isothiocyanates and indoles	Cruciferous vegetables, e.g. broccoli, cabbage	Antimutagen
Allyl thiosulphinates	Garlic, onions, leeks	Anticarcinogen Antibacterial Cholesterol lowering
Terpenoids including limonene	Citrus, caraway seeds	Anticarcinogenic against mammary tumours
Phytosterols	Pumpkin seeds	Reduce symptoms of prostate enlargement
Curcumin	Turmeric	Anti-inflammatory
Salicylates	Grapes, dates, cherries, pineapple, oranges, apricots, gherkins, mushrooms, capsicums, zucchini	Protective against macrovascular disease Modulation of gene expression
L-dopa	Broad beans	Treatment of Parkinson's disease
Non-digestible carbohydrates	Artichoke, chicory root murrnong, maize, garlic, oats, fruit and vegetables	Stimulate growth of microbial flora Cholesterol lowering

The antioxidant properties of red wine may contribute to a reduced risk of coronary heart disease

Red wine is a significant source of flavonoids in the diet of some cultures and its antioxidant properties may contribute to a reduced risk of coronary heart disease in wine drinkers even though the saturated fat intake is not low – the so-called 'French paradox'. A recent epidemiological study from the Netherlands by Hertog and associates has demonstrated a reduced risk of coronary heart disease associated with increased ingestion of dietary flavonoids in men.[3,4]

Isoflavonoids, another group of plant polyphenolic compounds, occur principally, although not exclusively, in legumes (Leguminosae family). They are at particularly high levels in certain legumes which are regularly consumed by humans and animals. Indeed many traditional diets which have relatively high legume consumption (soy, lentils, chickpeas, etc.) consequently have high isoflavone contents.[5] A small number of isoflavones, such as genistein and daidzein, display oestrogenic activity.[6,7] This hormonal effect is attributed to the similar spatial arrangement of functional groups on both isoflavones and oestrogens, allowing those isoflavones to bind to oestrogen receptors, especially the β-receptor.[8] Furthermore, genistein is also found to inhibit endothelial cell proliferation and in vitro angiogenesis.[9]

The average intake of all flavonoids in the US has been estimated to be 1g/person/day (expressed as glycoside).[10] However, much more recently Hertog and colleagues have reported that the flavonoid intake for Dutch elderly men was 25mg/day, using data on content of flavonoids (analysed by high pressure liquid chromatography [HPLC]) in vegetables, fruit, fruit juice, tea infu-

sions and wines.[4] The Japanese intake of flavonoids may reach 100–200mg/day.[11]

Polyphenols

A number of investigators have identified epigallocatechin gallate (EGCG) as the principal antimutagenic and anticarcinogenic compound in green tea. Beneficial effects of drinking tea have been observed in relation to blood pressure, serum cholesterol and other lipids.[12-14] The simultaneous intake of teas with food products that are being nitrosated within the stomach of human subjects could be protective against gastric cancer.[15]

Isothiocyanates and Organosulphides

Isothiocyanates, found in mustard oils, are widely distributed in plants, many of which are consumed by humans. They are responsible for the pungent and acrid flavour and odour of condiments such as mustard and horseradish and the familiar biting taste that develops when some cruciferous vegetables, such as broccoli, are eaten. Isothiocyanates have a variety of pharmacological and toxic activities. These include goitrogenic, antibacterial, antifungal and antiprotozoal actions. Several substances in this group could block the toxic and neoplastic effects of a wide variety of chemical carcinogens.[16]

Allyl thiosulphinate compounds, found in onions, leeks and garlic, enhance immune function

Allyl thiosulphinate compounds, found in onions, leeks and garlic, enhance immune function, increase the production of enzymes that help to catabolise carcinogens, decrease the proliferation of tumour cells, and reduce serum cholesterol.[17]

Monoterpenes

Limonene is a monoterpene found in the essential oils of citrus fruits, spices and herbs. Its content in orange peel ranges from 90 to 95%. Potential of limonene as a chemotherapeutic and chemopreventive agent for human breast and possibly other cancers is based on results of animal studies showing chemopreventive activity against mammary, skin, liver and lung tumours.[18,19]

Salicylates

Salicylates in food have mainly been of interest in work on food sensitivity.[20] However, the health protective effect from food salicylates may, in part, resemble the effects of acetylsalicylic acid (aspirin). Aspirin, of course, is interesting in terms of its action against macrovascular disease, such as coronary heart disease, stroke, and against neoplastic disease of the gut;[21] the same may be true of food salicylates. The functions of salicylates are likely to extend beyond the inhibition of prostaglandin synthesis to include modulating G-protein function and gene expression.[22,23]

L-Dopa

Patients with Parkinson's disease can benefit from meals of broad beans, and the response to *Vicia faba* beans may even be better than to conventional L-dopa medication in some cases.[24,25]

Phytochemical Toxicity

We know that the dose–response relationships for some phytochemicals, notably biogenic amines and salicylates, may be steep for some individuals, leading to 'food sensitivity'.[20] Tolerance may be greater in a varied diet with snacking than with large meals, since the intakes are in smaller aliquots and can be modulated by other factors.

Caution will be required where a large amount of a particular food source of phytochemicals is ingested for therapeutic effect, because toxic levels of the compound of interest may be reached along with those of other companion compounds, about which less is known.

Food Selection

Until recently, nutritionists have focused primarily on the nutrient elements in foods previously mentioned, and counselled that we consume a 'balanced diet'. With the interest in dietary fibre and new insights into many phytochemical components in foods, this perspective is becoming outdated. With opportunities for the cultural broadening of the human diet with more food items, interest in functional foods, probiotics (such as live *Lactobacillus* and *Acidophilus* cultures added to yoghurt), prebiotics (fructo-oligosaccharides, resistant starches) and in food restoration and fortification (e.g. with folic acid, dietary fibre), the public will require a greater level of nutritional literacy and logic.

A 'food and phytochemical approach' places emphasis on both nutrients and non-nutrients

A 'food and phytochemical' approach can be used to assess food intake in terms of the proportions and variety of food required to minimise risk of food-related disorders. Since it is not known exactly which food constituents are responsible for protection against chronic diseases, this approach places more emphasis on food, thus encompassing nutrients and non-nutrients, notably phytochemicals.

Table II. Phytochemical-dense food checklist

This list is not exhaustive for phytochemicals.
Score 1 point for each food if eaten at least once in a week irrespective of serving size. If a food is consumed more often, it still scores only one.

Whole grains (unrefined) and cereals	
barley	
maize/corn	
millet	
oats	
rice	
rye	
sorghum	
wheat	
Fruit	
apples	
apricots	
other stone fruit, e.g. nectarines, peaches	
berries, e.g. strawberries	
citrus, e.g. orange, lemon, grapefruit	
figs	
currants and grapes, e.g. raisin, sultana	
kiwi	
melons	
pears	
paw paw	
other tropical fruit, e.g. mango, pineapple	
Vegetables	
artichoke	
avocado	
broccoli/cabbage/brussels sprouts/cauliflower	
capsicum (red or green)	
carrots	
cucumber	
chilli	
fresh garlic	
onions/leeks	
potatoes	
pumpkin	
radish	
Running Total	

rhubarb	
swede	
sweet potatoes	
tomatoes	
yams	
dark green leafy vegetables, e.g. spinach, endive, amaranth, silverbeet	
light green leafy vegetables, e.g. lettuce	
Legumes/pulses	
soy beans/soy products, e.g. tofu, soy milk	
chickpeas	
lentils	
peas	
beans, e.g. kidney, haricot	
Nuts and seeds	
linseed	
sesame seed	
pumpkin seed	
nuts, e.g. peanuts, hazelnuts	
Herbs and spices	
basil	
oregano	
mint	
dill/fennel	
parsley	
pepper	
ginger	
cumin	
turmeric	
coriander	
rosemary/thyme	
Beverages	
fresh fruit juice	
red wine	
tea (green or black)	
herb tea	
Oils	
olive oil (unrefined)	
Total	

This has been adapted from Savige et al.[30]
This checklist has been left white so that it can be easily photocopied

A food guide which encompasses this approach is not currently available. Until more unequivocal evidence is obtained, a modification can be made using the Healthy Eating Pyramid (formerly called Healthy Diet Pyramid) of the Australian Nutrition Foundation and increasing the variety of fruit and vegetables. The phytochemical adequacy of the diet can be assessed to some extent by the food variety score (Table II). This score does not provide guidance about the desirable weekly intake of phytochemically dense foods such as certain fruits (e.g. berries, watermelon, apples), vegetables (e.g. tomatoes, onions, garlic), legumes (e.g. soy, chickpeas), nuts/seeds (e.g. linseed, sesame), tea and herbs (e.g. oregano, mint, dill). The higher the score, the more adequate the diet will be in phytochemicals; however food scores need to be further developed.

Eating a wide variety of foods appears to maximise the potential benefits of biodiversity

A wide variety in the diet appears to confer some protection against macrovascular disease, obesity, diabetes and possibly even cancer.[26-29] This provides an advantage while nutrition science is evolving and uncertainty exists about the potential benefits that particular foods and their complex components (including phytochemicals) may confer. No single food can provide a nutritious and healthy diet, except for human milk in the first few months of life. For the human species, eating a wide variety of foods appears to maximise the potential benefits of biodiversity, particularly of plant foods, whilst diluting any potentially toxic constituents. Foods from these various sources can be scored and the total score used as an indicator of the adequacy of the diet.[30]

Current Therapeutics

Nutrition and Phytochemicals: the Paradigm Shift

Over the past decade interest in health foods and natural therapies has resulted in many people preferring to diagnose and self-medicate for common or chronic health complaints. A survey in South Australia in 1993 showed that 48.5% of 3004 persons aged 15 or older use at least one non-medically prescribed alternative medicine, excluding calcium, iron and prescribed vitamins. It was also extrapolated that the cost to the Australian population for alternative medicines was A$621 million, and the cost for alternative therapists A$309 million per annum.[31]

With increasing use of health promoting foods and phytotherapy by the general public and opinion increasingly being sought from healthcare practitioners about their effectiveness, there is an urgent need for well conducted 'clinical studies with clear definitions of dosages and effects'.[32]

The health promoting use of plants has been known in food cultural folklore for many centuries, but identification of active phytochemical principle(s), clear understanding of mechanisms of action and reproducibility of proposed therapeutic benefits have not been as easy to demonstrate. New analytical technology and advances in molecular biology have identified phytochemical components of popular foods used in health promotion which may explain traditional health benefits and help quantify possible health benefits.

A problem in considering the place of phytochemicals in human health is that they are numerous, alongside a few known essential nutrients, and, therefore, their net interactive effect ultimately requires a study of food itself and food patterns[33], or that the intake of food components be subjected to sophisticated mathematical modelling. However, the advent of advanced informatics may help resolve this dilemma.

When particular bodily functions or disease processes are considered alongside the phytochemical or other non-nutrient food components which may modulate them, the potential for making better use of basic

food commodities and of relevant functional foods becomes apparent. For example, products might be designed to prevent or to manage obesity through altering appetite, the sensory response to food (taste, smell, look, texture and sound in eating) or energy utilisation.[34] Such development will, however, need to take into account the caveats to which reference has been made.

The nutritional trend is increasingly to use protective foods to prevent and manage diseases rather than depend so heavily on exclusion of detrimental items. This may equally be the focus of prevention and management of phytochemical deficiency. CT

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All the authors have interests in biologically active substances in food and how they affect human health, and the effect of migration on traditional diets, and also effects on health and mortality.

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