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Demystifying Phytochemicals: An Insight

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Abstract: Evidence is growing that bioactive substances found in a variety of plant-derived foods have the potential to reduce the risk of chronic diseases, such as cardio vascular disease and cancer. These substances can be categorized as: flavonoids and allied phenolic and polyphenolic compounds, terpenoids, alkaloids and sulphur-containing compounds. Much of the evidence collated to date is derived from animal studies, *in vitro* experiments and *ex vivo* studies in humans. Work should focus on their bioavailability in humans and the quantity required for their beneficial effects.

Key words: Flavonoids and allied compounds, chocolate, phytochemicals, terpenoids, alkaloids and sulphur containing compounds

INTRODUCTION

It has been recognized for some time that diets rich in fruits and vegetables are generally associated with a lower risk of chronic disease: particularly coronary heart disease and stroke[1], cancer[2], age-related eye conditions and chronic lung disorders[3].

The search initially focused on the so-called antioxidant nutrients (e.g. vitamins C and E and β-carotene). Observational studies have produced promising and consistent results. However, consistent and convincing evidence has eluded researchers in intervention trials using supplements[3].

Attention has turned to diverse other constituents in edible plant foods, such as flavonoids, carotenoids and sulphur-containing compounds. These are known collectively as phytochemicals or plant bioactive substances. These substances potential to improve health has been the subject of a British Nutrition Foundation Task Force[4].

It is the phytochemicals in, for instance, tea, broccoli and tomatoes that have captured headlines such as ketchup could help to fight off breast cancer; sage may reduce memory loss. How eating greens may stop children wheezing.

Why are these substances present in plants?: These bioactive substances have various roles in plant metabolism and its interaction with the environment. Phytochemicals provide colour to stems, leaves, flowers and fruits, they attract pollinating insects and seed-dispersing animals; some have antifungal and antibacterial properties, providing resistance to disease; still others act as deterrents against attack by insects and other predators (including man). The latter property reinforces the point that just because a substance is natural, doesn't automatically mean it is safe. Indeed, members of the alkaloid family of phytochemicals, which are widely dispersed in the plant kingdom, were active ingredients in poisons and potions used across the centuries. Many are still in use today as prescription medicines, e.g. atropine and codeine, whilst others are the active ingredients in drugs, such as opium and cocaine.

Many tens of thousands of plant bioactive substances have been identified[4]. These can be classified into three broad groups (Fig. 1).

1. Flavonoids and allied phenolic and polyphenolic compounds (about 8000 are known to exist).
2. Terpenoids: e.g. carotenoids and plant sterols (about 25000 terpenoids have been identified).
3. Alkaloids (there are about 12000) and sulphur-containing compounds: glucosinolates found in sprouts, broccoli and other members of the Brassica family and derivatives of the sulphur amino acid cysteine, found in the onion family.

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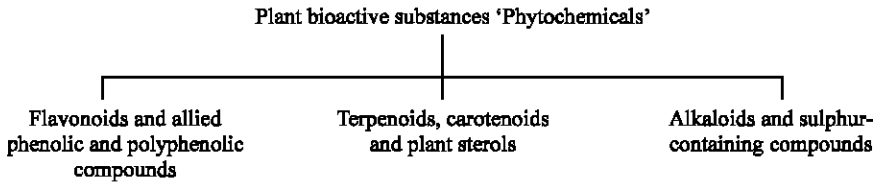

Fig. 1: Categories of plant bioactive substances

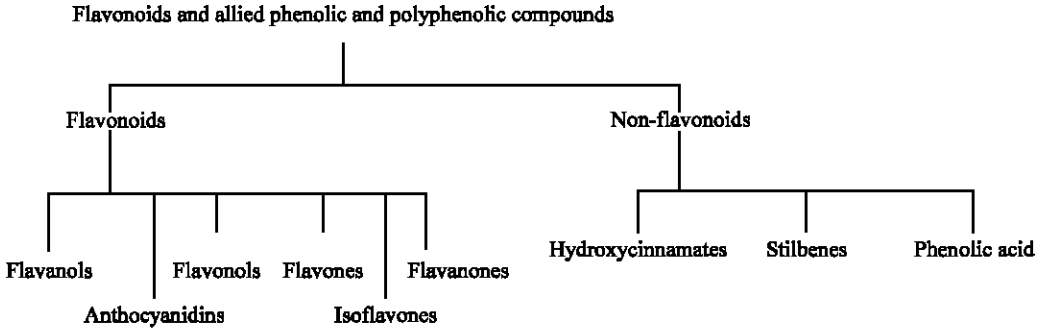

Fig. 2: Types of flavonoids and allied compounds

Flavonoids and allied phenolic substances: The Flavonoids are the most numerous of the phenolics and are found throughout the plant kingdom, concentrated mainly in the epidermis of leaves and the skin of fruit and in derived products such as tea, chocolate and olive oil. This group includes:

- Flavanols including catechins, their derivatives and proanthocyanidins or procyanidins, found in tea, apples, apricots, cherries, cocoa and chocolate.
- Flavonols, including quercetin and myricetin found in onions, apples, broccoli, cherries and berries and tea
- Flavones are found in parsley, thyme and celery.
- Flavones including hesperidin and naringen found in citrus fruit.
- Anthocyanidins, such as cyaniding found in red and purple fruits such as grapes and cherries.
- Isoflavones (also known as phytoestrogens), such as soya protein products also found in other legumes to a lesser extent.

The principal non-flavonoid compounds in this group are the hydroxycinnamates (caffeic acid and ferulic acid), stilbenes (another type of phytoestrogen) and phenolic acids (tannins).

Flavonoids account for about two-thirds of current dietary phenol intake, which is estimated to be about one gram per day in total, with phenolic acids accounting for the remainder. The main dietary sources of flavonoids are fruits, beverages (fruit juice, tea and cocoa) and chocolates. Tea is by far and away the greatest contributor to flavanol intake[5]. It provides 65% of a total intake of 25.5 mg per day in children and 83% of a total intake of 55.6 mg per day in adults (19-64 years). In children, the next major contributor was chocolate (20%). In adults, 5.6% of intake came from chocolate and roughly equivalent amount (5.9%) from apples/pears. In older adults (>65 years), who has total intake of 75.1 mg per day, the proportions were 87% (tea), 2.6% (chocolate) and 5.3% (apples/pears).

Proposed health effects: Research on flavonoids initially focused on possible direct antioxidant effects, e.g., whether they can inhibit oxidation of LDL (considered an important step in the development of atherosclerosis) or protect DNA from oxidative damage (important in cancer prevention). But the scope has now been broadened to include anti-inflammatory properties.

Platelet activation and aggregation are recognized characteristics of an increased tendency for blood to clot and may also be involved in the progression of atherosclerosis. The impact of various flavonoids on this system has been investigated and it is of interest that, as might be expected, effects were seen with beverages, chocolate, which differ in the types of flavanols they contain[4,6].

Bioavailability: It is undeniably important to find out how phytochemicals confer a protective effect. However, we

first need to identify whether or not they are absorbed into the circulation or are capable of reaching the tissues of interest.

Plasma levels of many of the substances of interest (e.g., some of the catechins derivatives) increase after they have been eaten[4]. The total antioxidant capacity of the plasma can also increase following consumption of these bioactive substances.

It will now be apparent that, even among the flavonoids, there are many dietary options in particular, chocolate features on the list of sources of flavonoids. Chocolate's flavonoids are derived from the cocoa bean, which is a major ingredient of chocolate[7]. Flavonoids account for between 14 and 18% of the weight of the raw cocoa bean. Cocoa polyphenols inhibit LDL oxidation, platelet activity and inflammatory agents *in vitro* and induce smooth muscle relaxation. Plasma levels and antioxidant capacity increase following consumption of cocoa flavonoids. Furthermore, extracts of tea have been shown to have a number of similar effects. Compared to tea, less work seems to have been done on the specific health effects of fruit and vegetable flavonoids, although similar *in vitro* effects might be expected. But before health benefits of any of these substances be established with certainty, more work is needed to estalish their effects in humans when consumed as part of a normal diet. Also, as with all things, moderation is the key. As well as being a source of flavonoids and a number of micronutrients, chocolate is a source of fat (cocoa fat is less rich in the types of fat that raise blood cholesterol than some other sources of dietary fat).

Terpenoids: Members of this group include the carotenoids. The five most commonly occurring carotenoids in the blood are β-carotene, lycopene, lutein, β-cryptoxanthin and α-carotene. The main dietary sources of these are respectively, carrots, tomatoes tomato products, peas and citrus fruit[8]. Average total intake in adults is 12-14 mg per day, mainly β-carotene and lycopene[8].

There is a strong rationale for a protective association between carotenoid intake and cancer. The majority of 28 epidemiological studies reviewed by Ziegler *et al.*[9] showed that lung cancer risk is reduced with increased intake of carotenoids (and fruit and vegetables). However, intervention studies with β-carotene among individuals at high risk of lung cancer (heavy smokers) indicated that supplements actually increase the death rate from this disease. Furthermore, a recent meta-analysis of randomized controlled trials with β-carotene supplements, revealed a small but significant increase in all causes of mortality[10]. These findings suggest that, whilst dietary levels of β-carotene, a precursor of vitamin A, are of potential benefit, higher intakes (as supplements) may have adverse effects. This is just one example of the frequent-finding in mutation that its indeed possible to have too much of a good thing.

An inverse association between lycopene, found in tomatoes and prostate cancer has been reported in the USA but provisional data from the large European Prospective Investigation into Cancer and Nutrition (EPIC) study does not support this association[11]. Also in the terpenoid group are plant sterols, which have gained fame through their proven ability, in the form of plant sterol and stanol esters, to reduce plasma cholesterol levels when incorporated into foods such as spreads[4]. Reductions in LDL-cholesterol of 10-15% have been reported when products containing phytosterols/ phytostanols are consumed periodically over the day, for a period of time. Their action hinges on their very low absorption rates and their structural similarity to cholesterol and hence their competition in the gut with dietary and endogenous cholesterol, reducing uptake of cholesterol and facilitating its elimination from the body.

Alkaloids: There are around 12000 alkaloids in the plant world, some of which are present in plants used as foods and are presumably there to discourage attack by microorganisms, insects and herbivores. For example, glycoalkaloids are present in green and sprouting potatoes, consumption of which can result in nausea and vomiting.

Glucosinolates: Brassica vegetables, such as sprouts, broccoli and cabbage, contain sulphur compounds known as glucosinolates, which have been shown in test systems, such as *in vitro* experiments, to induce potentially anti-carcinogenic defence mechanisms. At least part of their effect seems to be due to their metabolism in the colon by gut bacteria. Biologically active breakdown products (isothiocyanates) are released, which interact with colonic epithelial cells and enter the circulation via the colonic mucosa.

A paradox exists: it is the glucosinolates that give sprouts and other brassicas their characteristic taste, which is not universally popular. Any attempts to modify the glucosinolate content to improve flavour needs to take this paradox into account. Glucosinolates are also responsible for the hot spicy flavour of radish, rocket and watercress.

Other sulphur-containing compounds: Onions and garlic, members of the *Alliaceae* family, have been an important

part of the human diet for the thousands of years. Sulphur-containing compounds (S-alkyl cysteine sulphoxides) are found in all varieties, along with flavonols such as quercetin. It has been suggested that the sulphur-containing compounds allicin and ajoene are responsible for claimed health benefits of garlic, but there is limited evidence to substantiate this view[4].

Although it is not yet possible to pick out individual plant components as being more important than others, or indeed individual plant foods, the fact remains that diets rich in plant food are associated with better health. So, including at least five 80 g servings of fruit and vegetables in the daily diet is as important as ever. There are thousands of bioactive substances present in plant foods and some (e.g. the glucosinolates) are found in a relatively narrow range of foods. Some constituents may eventually prove to be of particular importance for human health, but these have yet to be identified.

This emphasis on plant foods shouldn't be interpreted as a need to become vegetarian or even vegan. Although such diets can be healthy, they still need to be carefully balanced in order to provide the nutrients naturally present in sub-stantial amounts in animal-derived foods, e.g. iron, zinc and vitamin B12 in meat; calcium, vitamin B12 and ribo flavin in milk and its products. These animal-derived foods also provide other substances such as Conjugated Linoeic Acid (CLA), which is only present in milk and meat from ruminant animals and for which a whole range of potential benefits has been proposed[12].

Another aspect that should not be underestimated is the difficulty associated with trying to encourage people to change their diets. Evaluation of a national fruit and vegetables campaign in the USA has demonstrated that it is easier to increase fruit than vegetables, though increases were modest even for fruits[13]. This suggests that different strategies may be needed of fruit and for vegetables. It is important that these also meet general healthy-eating guidelines, e.g. with respect to salt and fat content.

Phytoestrogens: Phytoestrogens are plant substances that bear a structural similarity to mammalian oestrogen. Isoflavones are the main phytoestrogens, but other examples include lignans (found in cereal seeds and vegetables) and stilbenes. Much of the interest in the phytoestrogens lies in their ability to exert weak hormone-like activity and stems from the observation that women consuming a traditional Japanese diet, rich in soya Isoflavones, report fewer menopausal symptoms and have lower rates of common disease such as heart disease, breast cancer and osteoporosis. A key issue that is still to be resolved is whether intake has to be life long (as in traditional Japanese diets) to exert its full effect.

Isoflavone-rich foods (though not isoflavone supplements) have been shown to have a beneficial effect on hot flushes that exceeds placebo, although the impact is much less than that seen with Hormone Replacement Therapy (HRT). Soya has a modest ability to reduce plasma cholesterol levels provided that both the soya protein and the isoflavones are present. The data with regard to bone health are still unclear and the balance of risks versus benefits of phytoestrogens in relation to breast cancer remains unresolved.

This work needs to be corroborated in humans using quantities that are relevant to feasible levels of intake from foodstuffs. Further research should focus on identifying the mechanisms of action of these substances, their bioavailability in humans and the quantity required to affect benefit.

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