Phytochemicals and cancer

Ian T. Johnson
Institute of Food Research, Norwich Research Park, Colney, Norwich NR4 7UA, UK

Epidemiological studies showing a protective effect of diets rich in fruits and vegetables against cancer have focused attention on the possibility that biologically-active plant secondary metabolites exert anti-carcinogenic activity. This huge group of compounds, now collectively termed ‘phytochemicals’, provides much of the flavour and colour of edible plants and the beverages derived from them. Many of these compounds also exert anti-carcinogenic effects in animal models of cancer, and much progress has been made in defining their many biological activities at the molecular level. Such mechanisms include the detoxification and enhanced excretion of carcinogens, the suppression of inflammatory processes such as cyclooxygenase-2 expression, inhibition of mitosis and the induction of apoptosis at various stages in the progression and promotion of cancer. However, much of the research on phytochemicals has been conducted in vitro, with little regard to the bioavailability and metabolism of the compounds studied. Many phytochemicals present in plant foods are poorly absorbed by human subjects, and this fraction usually undergoes metabolism and rapid excretion. Some compounds that do exert anti-carcinogenic effects at realistic doses may contribute to the putative benefits of plant foods such as berries, brassica vegetables and tea, but further research with human subjects is required to fully confirm and quantify such benefits. Chemoprevention using pharmacological doses of isolated compounds, or the development of ‘customised’ vegetables, may prove valuable but such strategies require a full risk–benefit analysis based on a thorough understanding of the long-term biological effects of what are often surprisingly active compounds.

Phytochemicals: Anti-carcinogenic activity: Molecular effects: Chemoprevention

A review by the author and colleagues was published in 1994 (Johnson et al. 1994) that explored the potential anti-carcinogenic effects of a range of biologically-active secondary plant metabolites commonly present in human diets, and tentatively considered whether such compounds, now commonly referred to collectively as ‘phytochemicals’, might usefully be regarded as a new class of micronutrients. The interest in these compounds was stimulated partly by the work of pioneers in this field such as Wattenberg (1975a,b), who first demonstrated the principles of chemoprevention by plant constituents in animal models, and partly by the wealth of epidemiological evidence then emerging for protective effects of diets rich in fruits and vegetables against a variety of cancers (Block et al. 1992). A great deal of new evidence has become available in the last decade, and awareness of the importance of plant foods in the prevention of chronic disease in general has grown (Daveilas et al. 2005; Houston et al. 2005; He et al. 2006). The aim of the present paper is to review some important aspects of emerging knowledge about the anti-carcinogenic effects of plant secondary metabolites at the cellular and molecular levels, and to reappraise the overall importance of these compounds and their metabolites in human nutrition. To begin with, however, it will be useful to consider briefly the most recent epidemiological evidence for anti-carcinogenic effects of fruits and vegetables.

Cancer, plant foods and human diets

Much of the earliest evidence for protective effects of fruits and vegetables against cancer was based on case–control studies. In an important review Block and colleagues (Block et al. 1992) summarised the available evidence and showed that after controlling for confounding factors, individuals in the lowest population quartile for fruit and vegetable intake experienced about twice the risk of cancer compared with those in the highest quartile.

Abbreviations: COX, cyclooxygenase; GST, glutathione S-transferase; ITC, isothiocyanate; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.
Corresponding author: Professor Ian Johnson, fax +44 1603 255330, email ian.johnson@bbsrc.ac.uk
A few years later Steinmetz & Potter (1996) came to a similar conclusion, and the World Cancer Research Fund (1997) major study, Food, Nutrition and the Prevention of Cancer, found ‘convincing’ evidence for protective effects of fruits and vegetables against cancers of the upper aerophageal tract, stomach and lung, and of vegetables against cancers of the colon and rectum. Since the turn of the millennium, however, there appears to have been a shift in opinion toward the view that the evidence is less strong than originally thought, mainly because several large prospective studies focusing on the main causes of cancer in Western countries have found either no protective effects (Michels et al. 2000; Smith-Warner et al. 2001) or weaker effects than those expected on the basis of previous case–control studies (Terry et al. 2001; Smith-Warner et al. 2003). The recent publication of results on breast and prostate cancer derived from the European Prospective Investigation into Cancer and Nutrition (Key et al. 2004; van Gils et al. 2005) suggests that this trend is continuing.

The most comprehensive summary of the field currently available is probably that of the International Agency for Research on Cancer (2003), which has concluded that: ‘There is limited evidence for a cancer-preventive effect of consumption of fruit and of vegetables for cancers of the mouth and pharynx, oesophagus, stomach, colon-rectum, larynx, lung, ovary (vegetables only), bladder (fruit only) and kidney. There is inadequate evidence for a cancer-preventive effect of consumption of fruit and vegetables for all other sites’. Nevertheless, although both the perceived size and statistical significance of the anti-carcinogenic effects of diets rich in fruits and vegetables have diminished with the passage of time, interest in the biological effects of their constituents has grown. The emerging evidence for a variety of potentially important anti-carcinogenic mechanisms has stimulated interest in the broad concept of chemoprevention, focused attention on particular fruits and vegetables rich in the most active compounds and encouraged a more mechanistic approach to epidemiology. Some of these issues will be discussed after the molecular effects of particular groups of phytochemicals have been reviewed.

### Blocking tumour initiation

Studies of the anti-carcinogenic effects of a variety of plants, plant constituents and synthetic chemopreventive agents led Wattenberg (1985) to define food-borne anti-carcinogens generally as either blocking agents, which act immediately before or during the initiation of carcinogenesis by chemical carcinogens, or suppressing agents, which act after initiation during the prolonged stages of promotion and progression. This framework has been valuable for the development of research on the many different types of secondary plant metabolites that show biological activity in mammals (Johnson et al. 1994), and it continues to provide a valuable approach to the classification of these compounds and their effects. A scheme for the interactions between blocking agents, suppressing agents and the generalised sequence for the onset of neoplasia is shown in Fig. 1.

### Modulation of carcinogen metabolism

Blocking agents prevent genotoxic carcinogens from forming adducts with DNA, either by inhibiting their activation from procarcinogens or by enhancing their detoxification and excretion. These actions are thought to be achieved primarily through the modulation of phase I and phase II metabolic enzymes in the gut, liver and other tissues exposed to the environment. Phase I metabolism involves the oxidation, reduction and hydrolysis of xenobiotics, including drugs, toxins and carcinogens,
principally by the cytochrome P450 enzymes (Nelson et al. 1993). The products of phase I metabolism are often highly-reactive genotoxic intermediates that form substrates for phase II enzymes such as glutathione S-transferase (GST), NAD:quinone reductase and \( \gamma \)-glutamylcysteine synthetase, which then catalyse the formation of less-reactive water-soluble conjugates. These conjugates are then readily excreted via the kidneys or in bile. Certain anti-carcinogenic phytochemicals induce transcriptional activation of phase I and II enzymes, via the xenobiotic response element and the antioxidant response element respectively. The so-called monofunctional inducers are those that interact primarily with the antioxidant response element, and hence selectively induce phase II enzymes, without simultaneously inducing activation of carcinogens via increased phase I activity (Prochaska & Talalay, 1988). The mechanism of induction is thought to be triggered by cellular stress, which leads to activation of intracellular protein kinases favouring the translocation of the transcription factor NF-E2 p45-related factor-2 to the nucleus, where it binds to the antioxidant response element and up regulates transcription (Itoh et al. 1997). Recent findings have shown that a second transcription factor, the ary1 hydrocarbon receptor, interacts directly with the NF-E2 p45-related factor-2 promoter, and that this functional link contributes to the coupling of phase I and II enzymes as an integrated system (Miao et al. 2005).

Several groups of phytochemicals have now been identified as potent inducers of phase II enzymes; two of the most actively investigated are the flavonoids, including epigallocatechin gallate, which is the principal biologically-active component of green tea (Chou et al. 2000), and the glucosinolate breakdown products, derived from cruciferous vegetables and herbs. Glucosinolates, of which >100 have been identified, are water-soluble glycosides containing a common S moiety and a variable side chain. They are found in cruciferous plants, a large and diverse group that contains mustard (Brassica juncea), rocket (Eruca sativa), radishes (Raphanus sativus) and the brassica vegetables (Mithen et al. 2000). Intact glucosinolates are biologically inactive and remain sequestered within cells throughout the plant. However, when the raw tissues are mechanically disrupted, the glucosinolates come into contact with the endogenous enzyme myrosinase and undergo hydrolysis, yielding an unstable intermediate that can give rise to a variety of active products (Mithen et al. 2000). Depending on the structure of the parent glucosinolate and the ambient conditions, these active products include isothiocyanates (ITC), nitriles, cyanoo-epithioalkanes and thiocyanates (Lambrix et al. 2001). In addition, the indolyl glucosinolates give rise to the indole-3-carbinols, which also induce detoxifying enzymes and act as anti-carcinogens in animal models (McDanell et al. 1988). Glucosinolate breakdown products can be formed in food processing, during digestion of uncooked vegetables in the upper gastrointestinal tract (Rouzaud et al. 2004) and by exposure to bacterial myrosinase in the colon (Rouzaud et al. 2003). Fig. 2 illustrates the release of glucosinolates in the gut lumen, the uptake and metabolism of the isothiocyanates and some possible sites of action and routes of excretion. The ITC sulforaphane, derived from broccoli (Brassica oleracea), acts via the NF-E2 p45-related factor-2 pathway (McWalter et al. 2004) and is amongst the most active food-borne monofunctional inducers yet identified (Talalay & Fahey, 2001).

A considerable amount of work has also been done to explore the importance of these effects at the whole organism level by studying carcinogen metabolism in animal models and in human subjects exposed to carcinogens from cigarette smoke. Both indole-3-carbinol and phenethyl ITC have been shown to modify the metabolism of the tobacco smoke carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in rodent models and inhibit the development of lung tumours, although their mechanisms of action differ. Indole-3-carbinol induces hepatic \( \alpha \)-hydroxylation of NNK, thus reducing the delivery of NNK to the lung (Morse et al. 1990), whereas phenethyl ITC inhibits \( \alpha \)-hydroxylation, and hence adduct formation in lung tissue (Hecht et al. 1996). The shunting of NNK metabolism away from the lung leads to increased hepatic metabolism and higher urinary excretion of NNK metabolites. Increased urinary excretion of two such metabolites, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and [4-(methylnitrosamino)-1-(3-pyridyl)but-1-yl]-\( \beta \)-\( \delta \)-glucosiduronic acid in human smokers consuming approximately 170 g watercress (Rorippa nasturtium-aquaticum)/d for 3 d suggests that a similar mechanism occurs in human subjects (Hecht et al. 1995). Hecht and co-workers (Hecht et al. 2004) have recently conducted a study of NNK metabolites in Singapore Chinese smokers and have reported an inverse correlation between cruciferous vegetable consumption and excretion of NNK metabolites that appears consistent with the known metabolic effects of indole-3-carbinol. Overall, the experimental and epidemiological evidence supports the conclusion that glucosinolate breakdown products modulate phase II metabolism in man, although the contribution of this mechanism to the putative anticarcinogenic effects of cruciferous vegetable consumption remains to be fully established.

Suppressing tumour progression

Once the critical genetic damage has occurred, the next stages in the development of neoplasia are the acquisition of further mutations and epigenetic marks that cause progressively abnormal gene expression. This progression is the promotion stage of cancer development, characterised by poorly-regulated cell proliferation and differentiation, and a reduced tendency for damaged cells to undergo apoptosis. Eventually, the cancer phenotype emerges at one or more discrete sites. There are many stages at which this complex process might start, be slowed or interrupted, and a correspondingly large number of plausible mechanisms for tumour suppression. Chemoprevention, the use of drugs or natural compounds at pharmacological levels to inhibit the development of cancer, is currently attracting a great deal of interest, particularly in the USA, but many of the same mechanisms may be triggered by phytochemicals occurring in substantial quantities in human diets.
Inflammation and cancer

It has long been recognised that inflammation is a risk factor for certain cancers (Balkwill & Mantovani, 2001). One obvious example is the increased risk of colo-rectal cancer associated with inflammatory bowel disease (Ekbom et al., 1990), but there are other examples of the involvement of inflammatory processes in the initiation and progress of cancer both within (Macarthur et al., 2004) and beyond the alimentary tract (Askling et al., 1999). There is also circumstantial evidence that chronic systemic inflammation, associated perhaps with the adverse metabolic factors now so common in prosperous Westernised societies (Johnson, 2005), may be a key driver for cancers of the alimentary tract (Karin et al., 2002).

A host of phytochemicals, including resveratrol, limonene, glycyrrhizin, gingerol, indole-3-carbinol, genistein, apigenin and many others, have been shown to inhibit NF-κB activity at various different stages in its regulatory pathway. For example, curcumin, a widely-studied anti-carcinogenic plant metabolite found in the spice cumin (Cuminum cyminum), suppresses TNF-induced activation of IκB kinase (Singh & Aggarwal, 1995), whereas caffeic acid phenethyl ester specifically prevents binding of NF-κB to its target DNA sequence (Natarajan et al., 1996). The downstream effects of NF-κB inhibitors include reduced expression of the key pro-inflammatory enzymes inducible NO synthase and cyclooxygenase (COX)-2.

NF-κB

NF-κB is a collective term for a family of dimeric proteins that act as transcription factors. In its inactive form NF-κB resides in the cytoplasm as a complex with the regulatory protein IκB. The activation pathway for NF-κB involves phosphorylation, of IκB by IκB kinase, leading to ubiquitination and proteolysis of IκB. This step frees NF-κB to translocate to the nucleus, where it binds to the κB sequence motif in DNA and acts as a transcription factor for at least 200 genes involved in the regulation of inflammation, cell proliferation, differentiation and apoptosis. NF-κB is constitutively activated in many tumours, and its key role as an up-regulator of inflammation suggests that it plays a key role in the earliest stages of promotion and progression (Karin et al., 2002).

Fig. 2. Glucosinolates are broken down by myrosinase during food processing or during digestion, and isothiocyanates and other breakdown products are released into the lumen. Some remain unabsorbed and are eventually broken down by the gut microflora, but a substantial quantity of free isothiocyanates diffuse passively into the mucosal epithelial cells where they are rapidly conjugated with glutathione (GSH), and then partially secreted back into the gut lumen by P-glycoprotein (Pgp-1) and multi-drug-resistance protein (MRP-1). Some free and conjugated isothiocyanates enter the bloodstream, however, and become available to interact with target tissues before further metabolism and urinary excretion. GST, glutathione S-transferase.
Cyclooxygenase inhibitors

COX (PGH synthase) exists as two distinct isoforms; COX-1, which is constitutively expressed, produces PG essential to platelet aggregation and the maintenance of gastric mucosal integrity, whereas COX-2 is induced by tumour promoters and endogenous cytokines and produces PG involved in inflammatory processes. A third enzyme (COX-3) has been described that is a splice variant of COX-1, and its physiological role in man is not yet clear. Both COX-1 and COX-2 are inhibited by aspirin, an acetylated derivative of the secondary plant metabolite salicylate, originally isolated from willow (Salix alba). Both aspirin and salicylate irreversibly inhibit the COX enzymes by selectively acetylating the hydroxyl group of a single serine residue, and they both also suppress NF-kB by inhibiting IkB kinase activity (Yin et al. 1998).

There is abundant evidence that a number of flavonoids are COX-2 enzyme inhibitors (Baumann et al. 1980) and some (e.g. apigenin, chrysin and kaempferol) can suppress COX-2 transcription by mechanisms including activation of the PPARγ transcription factor (Liang et al. 2001) and inhibition of NF-kB expression (Liang et al. 1999). Importantly, COX-2 transcription is inhibited in vitro not just by quercetin aglycone, but also by its human metabolites quercetin 3-glucuronide, quercetin 3'-sulfate and 3'-methylquercetin 3-glucuronide, and both quercetin and quercetin 3'-sulfate also inhibit COX-2 enzyme activity (O’Leary et al. 2004).

Direct inhibition of mitosis: the Wnt signalling pathway

The Wnt proteins are extracellular signalling molecules involved in the regulation of cell proliferation via the β-catenin signal pathway (Kundu et al. 2006). The nineteen known Wnt genes code for cysteine-rich glycoproteins; these proteins are released into the extracellular milieu where they modulate β-catenin signalling in target cells, via the membrane receptors Frizzled and LDL receptor-related protein. The intracellular protein β-catenin regulates many aspects of cellular organisation, ranging from cytoskeletal structure to the regulation of cell proliferation and death (Wikramanayake et al. 2003). Levels of β-catenin in the cytoplasm are tightly regulated by a system of proteasomal degradation that begins when β-catenin forms a complex with the adenomatous polyposis coli protein and another scaffolding protein axin. This complex then associates with casein kinase I, which phosphorylates the N terminus of β-catenin, and glycogen synthase kinase 3β, which phosphorylates other β-catenin residues. The phosphorylated β-catenin molecule is then recognised by cytoplasmic β-transducin repeat-containing protein, which mediates its ubiquitination and degradation.

Wnt signalling plays an important role in gut formation during mammalian embryogenesis, and contributes to the maintenance of normal gut homeostasis in the adult. Disruption of Wnt signalling is a key abnormality during the development of cancers of the alimentary tract (Gregorieff & Clevers, 2005). In normal cells there is a relatively large and stable pool of inactive β-catenin associated with the cytoskeletal protein cadherin, and a small labile pool in the cytoplasm. However, in cancer cells the degradation pathway is often suppressed and the balance is altered in favour of the cytoplasmic pool. Active β-catenin migrates to the nucleus, where it activates the lymphoid enhancer factor/ T-cell factor family of transcription factors (T-cell factors 1, 3 and 4, lymphoid enhancer factor), freeing them from repression by groucho and histone deacetylase, and leading to the transcription of a variety of effector genes including C-myc, cyclin-D1, c-jun and COX-2. It is well established that synthetic COX-2 inhibitors, including indomethacin and aspirin, suppress β-catenin/T-cell factor-mediated gene transcription in colo-rectal carcinoma cells (Dihlmann et al. 2001), and sulindac reduces nuclear β-catenin accumulation in the adenomatous polyps of patients with familial adenomatous polyposis (Boon et al. 2004). Moreover, a number of phytochemicals, including quercetin (Park et al. 2005), which suppresses colo-rectal crypt cell proliferation in the rat in vivo (Gee et al. 2002), also interact with the β-catenin pathway in vitro (Jaiswal et al. 2002; Joe et al. 2002). Dashwood et al. (2002) have shown that green tea, a minimally-processed ‘white’ tea and physiologically-relevant levels of epigallocatechin gallate all suppress nuclear β-catenin/T-cell factor 4 activity in HEK293 (kidney) cells in vitro. In the APCmin model of colo-rectal cancer, in which the adenomatous polyposis coli protein is disabled by an APC mutation, treatment with white tea, green tea or the non-steroidal anti-inflammatory drug sulindac all suppress tumourigenesis (Orner et al. 2003). There was also evidence for suppression of β-catenin and its downstream products in the normal mucosa of mice treated with tea, and particularly in those treated with a combination of tea and sulindac.

Induction of apoptosis

Although the suppression of abnormal mitosis may slow the development of precancerous lesions and inhibit their competitive growth, the induction of programmed cell death can completely eliminate genetically-damaged cells from a tissue (Johnson, 2001). Several classes of phytochemicals, including organosulfur compounds (Xiao et al. 2005) from garlic (Allium sativum) and ITC, have been shown to induce apoptosis in cell lines. Although glucosinolate breakdown products act as powerful inducers of phase II enzymes and modulate carcinogen metabolism in vitro and in vivo, it is unlikely to be their only mode of action; there is also much interest in their ability to block mitosis and initiate apoptosis in a variety of epithelial cell lines and tissues. Oral administration of the pure glucosinolate sinigrin (Smith et al. 1998), the precursor of allyl ITC, or raw Brussels sprouts (Brassica oleracea var. gemmifera) rich in sinigrin (Smith et al. 2003) leads to an amplification of the apoptotic response occurring in colo-rectal crypts 48 h after exposure to the chemical carcinogen 1, 2 dimethylhydrazine. A high level of crypt-cell apoptosis is protective against colo-rectal neoplasia in both animal models (Chang et al. 1998) and human subjects (Martin et al. 2002). Importantly, the plasma and urinary metabolites to which the target tissues of human subjects are exposed in vivo may be just as effective as inducers of apoptosis as the parent ITC. Thus, the N-acetylcysteine conjugates of allyl ITC, benzyl ITC, phenethyl ITC and...
sulforaphane all readily inhibit proliferation and induce apoptosis in human bladder cancer cells (Tang et al. 2006). Furthermore, raw Brussels sprout juice exerts the same anti-proliferative effects as pure allyl ITC in vitro, yet contains no free allyl ITC (Smith et al. 2005). It is not entirely clear which of the other glucosinolate breakdown products and metabolites in raw Brussels sprout juice are responsible for this biological activity, but of those identified 1-cyano-2,3-epithiopropane, the gluconapin hydrolysis product, 3-butenyl isothiocyanate and the glucobrassicin metabolite ascorbigen are all candidates for this role. The mechanism of cell cycle arrest in vitro appears to involve a direct inhibition of tubulin polymerisation (Smith et al. 2004, 2005), but the involvement of this mechanism in the induction of apoptosis in vivo remains to be established.

Molecular epidemiology
One effect of the discovery that certain biologically-active constituents of plants exert anti-carcinogenic effects in model systems has been to focus the attention of epidemiologists on the particular fruits, vegetables and beverages that contain them. Interest in the area has also encouraged a more hypothesis-driven approach to epidemiology and the use of Mendelian randomisation to explore the effects of genetic polymorphisms on the consequences of particular dietary exposures (Davey Smith & Ebrahim, 2005). Studies on cruciferous vegetables provide some of the best examples of this trend, although the results are still rather ambiguous.

As mentioned previously, the GST superfamily contains a group of phase II detoxifying enzymes that metabolise environmental chemicals including carcinogens, drugs and phytochemicals. Approximately half the individuals in most human populations are homozygous for the null alleles of GSTT1 and GSTM1, and hence cannot express some important components of GST activity. These genotypes appear to carry little increased risk of lung cancer, but Lin et al. (1998) have hypothesised that the GSTM1 null condition might lead to a slower rate of metabolism of glucosinolate breakdown products. In high consumers of brassica vegetables this reduced rate of metabolism might be expected to enhance the exposure of target tissues to ITC, and hence confer greater protection against cancer. To test this hypothesis Lin et al. (1998) have conducted a case–control study of middle-aged patients undergoing screening sigmoidoscopy. A total of 459 cases having a first-time diagnosis of histologically-confirmed adenomas were compared with 507 controls with no polyp detected. Broccoli intake was assessed using a 126-item semi-quantitative FFQ. Subjects with the highest quartile of broccoli intake (3.7 servings per week) had an OR of 0.47 (95% CI 0.23, 0.95) for both alleles and consuming higher levels of cruciferous vegetables, the OR is 0.47 (95% CI 0.23, 0.95) compared with low consumers. Similar effects have been reported by London et al. (2000), working with another Chinese population in which exposure to cruciferous vegetables was determined subjectively using urinary excretion of ITC metabolites as a biomarker, and more recently by Brennan et al. (2005), who have studied a central European population.

Generally speaking, phytochemicals are rather poorly absorbed by human subjects, and are themselves rapidly metabolised by the phase II enzymes. Much of this metabolism occurs in the gut mucosa (Fig. 2), and a large proportion of the resulting conjugates are actively secreted back into the gut lumen (Petri et al. 2003). A recent study of the uptake and metabolism of the ITC sulforaphane from broccoli by human volunteers (Gasper et al. 2005) has demonstrated that in comparison with GSTM1-positive individuals those who are GSTM1 null excrete a greater proportion of the consumed dose of sulforaphane via the urine. They consider various possible explanations for this observation, and tentatively propose that expression of GSTM1 leads to retention of sulforaphane at some systemic site or sites, which facilitates its anti-carcinogenic...
activity. An alternative explanation may be that in the GSTM1-null individuals the absence of GSTM1 expression reduces the efficiency with which the ITC is transported back into the gut lumen following absorption (Petri et al. 2003); however, further studies will be needed to resolve this issue.

Conclusion

Whatever the final assessment of the overall contribution of diets rich in fruits and vegetables to cancer prevention turns out to be, there is no doubt that the phytochemicals they contain do exert a range of fascinating and potentially-important biological effects on human cells. One obvious weakness of the current state of research, however, is that much of it has been conducted in vitro, with little regard for the bioavailability of the compounds studied. In most cases the small proportion of any compound that is absorbed undergoes extensive metabolism before reaching target organs, and the products are readily excreted. Although such phytochemicals cannot be regarded in any meaningful way as nutrients, their beneficial side effects may well be exploited in chemoprevention, much as those of drugs are, either by using pharmaceutical delivery systems, or through the development of ‘customised’ vegetables with high levels of selected phytochemicals (Mithen et al. 2003). Such strategies will, however, require a full risk–benefit analysis, based on a thorough understanding of their overall biological effects.

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