

## Review

# Phytochemicals: nutraceuticals and human health

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**Abstract:** Phytochemicals, as plant components with discrete bio-activities towards animal biochemistry and metabolism are being widely examined for their ability to provide health benefits. It is important to establish the scientific rationale to defend their use in foods, as potential nutritionally active ingredients. Phytochemicals could provide health benefits as: (1) substrates for biochemical reactions; (2) cofactors of enzymatic reactions; (3) inhibitors of enzymatic reactions; (4) absorbents/sequestrants that bind to and eliminate undesirable constituents in the intestine; (5) ligands that agonize or antagonize cell surface or intracellular receptors; (6) scavengers of reactive or toxic chemicals; (7) compounds that enhance the absorption and or stability of essential nutrients; (8) selective growth factors for beneficial gastrointestinal bacteria; (9) fermentation substrates for beneficial oral, gastric or intestinal bacteria; and (10) selective inhibitors of deleterious intestinal bacteria. Such phytochemicals include terpenoids, phenolics, alkaloids and fiber. Research supporting beneficial roles for phytochemicals against cancers, coronary heart disease, diabetes, high blood pressure, inflammation, microbial, viral and parasitic infections, psychotic diseases, spasmodic conditions, ulcers, etc is based on chemical mechanisms using *in vitro* and cell culture systems, various disease states in animals and epidemiology of humans. However, it must be emphasized that a distinction needs to be drawn between the types of information that can be obtained from studies *in vitro*, in animals and in humans. Mechanisms of action must certainly be established *in vitro*; however, the efficacy of these same ingredients with their mechanisms of action, must also be demonstrated *in vivo*. The rapid growth in the use of phytochemicals in nutraceutical and functional foods requires that the food and pharmaceutical industries face new challenges: in addressing worldwide public concern over the efficacy and safety of supplements and foods claimed to be health-promoting; in government regulations related to safety, labeling and health claims for products that contain phytochemicals; in the manufacturing of foods with different qualities and stabilities; and in marketing issues, particularly as they relate to consumers' recognizing added value.

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## INTRODUCTION

A 'big bang' is currently impacting the food, health food and pharmaceutical industries, among others. This 'big bang' derives from an explosion in research and publications providing scientific evidence to support hypotheses that phytochemicals in foods and in isolated form provide health benefits to the consumer. No longer is 'an apple a day keeps the doctor away' a cliché quoted solely by persuasive mothers. As stated by Haslam<sup>1</sup> in reference to phytochemicals, 'There has been a big increase in interest in our ability to understand the importance of polyphenols in areas as diverse as agriculture, ecology and food selection, foodstuffs and nutrition, beverages (astringency and bitterness), natural medicines (the so-called 'French Paradox'), floral pigmentation,

natural glues and varnishes and the age-old methods for the manufacture of leather.' The diverse industries affected by increased knowledge of phytochemicals are delineated in this quotation.

The aim of this contribution is to review examples of recent, diverse laboratory evidence for protective and health-promoting effects of specific plant constituents, herein referred to as phytochemicals, that have the potential of being incorporated into foods or food supplements as nutraceuticals, or into pharmaceuticals, and to suggest implications of the explosion in information for the future development, discovery and use of phytochemicals as nutraceuticals. The term nutraceutical was coined by DeFelice, director of the Foundation for Innovation in Medicine.<sup>2,3</sup> A nutraceutical is any non-toxic food extract supplement that

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has scientifically proven health benefits for both disease treatment and prevention. In the context of this review, the term functional foods is used as defined by Roberfroid<sup>4</sup> as foods that 'should have a relevant effect on well-being and health or result in a reduction in disease risk.' The functional component of a functional food can be an essential macronutrient or micronutrient, a nutrient that is not considered essential or a non-nutritive component.

This review focuses on the health benefits of specific phytochemicals. As an example of evidence that supports such benefits, Steinmetz and Potter<sup>5</sup> reviewed 206 human epidemiological studies and 22 animal studies on the relation between vegetable and fruit consumption and risk of cancer. The protective effects of vegetables and fruits were evident for cancers of the stomach, esophagus, lung, oral cavity and pharynx, endometrium, pancreas and colon. Among the phytonutrients cited as potentially providing the protection were '... dithiolthiones, isothiocyanates, indole-3-carbinol, allium compounds, isoflavones, protease inhibitors, saponins, phytosterols, inositol hexaphosphate, vitamin C, D-limonene, lutein, folic acid, beta-carotene, lycopene, selenium, vitamin E, flavonoids, and dietary fiber.'

Some health benefits to animals and tissues are derived via cytotoxic actions. However, it is important to realize that the metabolic fate of most phytochemicals is poorly understood, and that absence of their toxicity to humans has not always been clearly demonstrated. The toxic nature of the phytochemicals reviewed is not discussed herein, but clearly, many plant constituents are toxic, having been developed through evolution for the specific purpose of plant self-preservation via toxicity to microbes, insects and other animals. Harborne<sup>6</sup> reviewed the following chemical barriers by which plants protect themselves via toxins: accumulation of toxins, induced accumulation of toxin, selective restriction of toxin synthesis to vulnerable tissues, a change in chemistry during ontogeny, production and accumulation of insect hormones or hormone-mimics, and variability of palatability among edible portions of the same plant. The reader who is interested in the toxicity of individual phytochemicals is referred to an excellent handbook on the subject by Duke.<sup>7</sup>

#### **PHYTOCHEMICALS: CLASSIFICATION AND HEALTH BENEFITS OF SELECTED PLANT CONSTITUENTS**

Harborne<sup>8</sup> identified the three major classes of plant chemicals as terpenoids, phenolic metabolites, and alkaloids and other nitrogen-containing plant constituents. As delineated by Harborne,<sup>8</sup> the terpenoids include monoterpenoids, iridoids, sesquiterpenoids, sesquiterpene lactones, diterpenoids, triterpenoid saponins, steroid saponins, cardenolides and bufadienolides, phytosterols, cucurbitacins, nortriterpenoids, other triterpenoids and carotenoids. The phenolic

metabolites include: anthocyanins, anthochlors, benzofurans, chromones, coumarins, minor flavonoids, flavonones and flavonols, isoflavonoids, lignans, phenols and phenolic acids, phenolic ketones, phenylpropanoids, quinonoids, stilbenoids, tannins and xanthenes. The alkaloids include: amaryllidaceae, betalain, diterpenoid, indole, isoquinoline, lycopodium, monoterpene, sesquiterpene, peptide, pyrrolidine and piperidine, pyrrolizidine, quinoline, quinolizidine, steroidal, and tropane compounds. Other nitrogen-containing constituents include: non-protein amino acids, amines, cyanogenic glycosides, glucosinolates, and purines and pyrimidines.

The intent of this review is to make reference only to those plant constituents that offer specific health benefits. The current literature has been surveyed to include reports of recently recognized health benefits of specific phytochemicals.

#### **Polyphenols**

Haslam,<sup>1</sup> in an excellent book entitled *Practical Polyphenolics*, wrote extensively and in detail about the structure, biosynthesis and classification of phenolic phytochemicals. Haslam<sup>1</sup> provided an interesting account of the history of man's use of phytochemicals, and followed the research trail for this branch of chemistry, biochemistry and technology. His approach to the book was based upon evaluation of the physical forces that underlie the 'molecular recognition' by polyphenols of other molecules. Plant polyphenols have a distinctive ability to form non-covalent, intermolecular complexes with each other and with both large and small molecules.

The largest group of phytochemicals comprises the phenolic chemicals. Plant polyphenols are secondary metabolites that are widely distributed in higher plants. Their distinguishing characteristics are: water solubility, molecular weights that range from 500 to 3000–4000 D, 12–16 phenolic groups and 5–7 aromatics rings per 1000 relative molecular mass, their intermolecular complexation, and their classification as condensed proanthocyanidins, galloyl and hexahydroxydiphenyl esters and derivatives, or phlorotannins.<sup>1</sup> Polyphenols historically have been considered as anti-nutrients by nutritionists, because some, eg tannins, have such adverse effects as decreasing the activities of digestive enzymes, energy, protein and amino acid availabilities, mineral uptake and having other toxic effects.<sup>9</sup> Recognition of the antioxidant activities of many polyphenols has realigned thinking toward the health benefits provided by many of these compounds.<sup>10</sup>

#### **Terpenoids (terpenes)**

The terpenes, also known as isoprenoids,<sup>11</sup> are the largest class of phytonutrients in green foods, soy plants and grains. The importance of terpenes to plants relates to their necessity to fix carbon through photosynthetic reactions using photosensitizing pigments. This dependence on photoreactive chemistry,

plus the inability of plants to move to avoid irradiation, places a strong reliance on a spectrum of phytochemical protectants from oxidative reactions. Animals have evolved to utilize these compounds for hormonal and growth regulatory functions (vitamin A) and, as it is now being understood, the presence of these molecules in animal tissues also provides a measure of protection from certain diseases, especially those related to chronic damage and growth dysregulation.

Terpenes have a unique antioxidant activity in their interaction with free radicals. Terpenes react with free radicals by partitioning themselves into fatty membranes by virtue their long carbon side chain. Perhaps the most studied of the terpene antioxidants are the tocotrienols and tocopherols.

#### *Tocotrienols and tocopherols*

Tocotrienols and tocopherols are terpenes that occur naturally in grains.  $\alpha$ -*d*-Tocopherol (vitamin E) has been extensively reviewed, and its role as vitamin E will not be discussed here. However, it is perhaps impossible to eliminate the obvious experimental confounding effects of tocopherol as vitamin E and its effects as a non-specific isoprenoid. The tocotrienols ( $\alpha$ ,  $\gamma$  and  $\delta$ ) and *RRR*- $\delta$ -tocopherol were effective apoptotic inducers for human breast cancer cells, whereas the tocopherols ( $\alpha$ ,  $\beta$  and  $\gamma$ ) and the acetate derivative of *RRR*- $\alpha$ -tocopherol (*RRR*- $\alpha$ -tocopheryl acetate) were ineffective.<sup>12</sup> The transport, tissue concentration and relative biological function of tocopherols and tocotrienols appear to be unrelated,<sup>13</sup> which may indicate that their effects on cancer cells *in vivo* are also different. In other studies,<sup>14</sup>  $\gamma$ -tocotrienol, a mixed isoprenoid, and  $\beta$ -ionone, a pure isoprenoid, suppressed the growth of diverse tumor cell lines via initiation of apoptosis and concomitant arrest of cells in the G1 phase of the cell cycle. The impact of a diet of fruits, vegetables and grains on reduction of cancer risk in part may be explained by the actions of terpenes *in vivo*.

#### *Carotenoids*

The carotenoid terpenes have been extensively studied as antioxidants.<sup>15-17</sup> These compounds are highly pigmented, being yellow, orange and red, are present in fruits and vegetables, and when consumed by birds are incorporated into the yolk of eggs. Carotenoids comprise two types of molecules, carotenes and xanthophylls.

Carotenes are tissue specific in their biological activity.  $\beta$ -Carotene,  $\alpha$ -carotene and  $\epsilon$ -carotene have vitamin A activity. The role of carotenoids as precursors to vitamin A will not be discussed here as this is a well-described and essential nutritional role for these molecules. However, the properties of these molecules to alter health independent of their functions as vitamin A precursors are now being studied intensively. As reviewed by Bendich,<sup>18</sup> the carotenes, including with  $\gamma$ -carotene, lycopene and lutein, protect against uterine, prostate, breast, colorectal and lung

cancers. They may also protect against risk of digestive tract cancer.<sup>19</sup> To be effective, lycopene must be absorbed and distributed to the tissues. Paetau *et al*<sup>20</sup> studied the uptake of carotenoids, including lycopene, by measuring changes in buccal mucosa cell content of the carotenoids following the oral delivery of 70–75 mg of lycopene in lycopene-rich tomato juice, tomato oleoresin, lycopene beadlets or a placebo. The lycopene level in these cells increased significantly after 4 weeks of ingestion of oleoresin or the lycopene beadlets, but not of tomato juice. There were also strong correlations between plasma and buccal mucosa cell concentrations of lutein,  $\beta$ -cryptoxanthin,  $\alpha$ -carotene and  $\beta$ -carotene, but not of lycopene.<sup>20</sup> The xanthophyll type of carotenoids offer protection to other antioxidants, and they may exhibit tissue specific protection.<sup>21,22</sup> Zeaxanthin, cryptoxanthin and astaxanthin are members of the xanthophyll group.

#### *Limonoids*

Limonoids are terpenes present in citrus fruit. Limonoids appear to provide chemotherapeutic activity by inhibiting Phase I enzymes and inducing Phase II detoxification enzymes in the liver.<sup>23</sup> *D*-Limonene, the commonest monocyclic monoterpene, found within orange peel oil, inhibits pancreatic carcinogenesis<sup>24</sup> induced in the hamster by *N*-nitrosobis(2-oxopropyl)amine and gastric carcinogenesis induced in Wistar rats by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.<sup>25</sup> Limonoids may also provide protection to lung tissue.<sup>26</sup>

#### *Phytosterols*

Phytosterols are another important terpene subclass. Two sterol molecules that are synthesized by plants are  $\beta$ -sitosterol and its glycoside. In animals, these two molecules exhibit anti-inflammatory, anti-neoplastic, anti-pyretic and immune-modulating activity. A proprietary mixture of  $\beta$ -sitosterol and its glycoside was tested *in vitro*, in animals and in human clinical trials.<sup>27</sup> The mixture targeted specific T-helper lymphocytes, the Th1 and Th2 cells, which improved T-lymphocyte and natural killer cell activity. Phytosterols were reported to block inflammatory enzymes, for example by modifying the prostaglandin pathways in a way that protected platelets.<sup>23</sup> Recently, the cytostatic activity of steroidal saponins from *Ruscus aculeatus* against leukemia HL60 cells was reported.<sup>28</sup>

In the body, phytosterols can compete with cholesterol in the intestine for uptake, and aid in the elimination of cholesterol from the body. Saturated phytosterols appear to be more effective than unsaturated compounds in decreasing cholesterol concentrations in the body.<sup>29</sup> These actions reduce serum or plasma total cholesterol and low-density lipoprotein (LDL) cholesterol. For example, a recent study showed that addition of blended phytosterols to a prudent North American diet improved plasma LDL cholesterol concentrations by mechanisms that did not result in significant changes in endogenous cholesterol

synthesis in hyper-cholesterolemic men.<sup>30</sup> Competition with cholesterol for absorption from the intestine is not unexpected as the structure of plant sterols is similar to that of cholesterol.<sup>29</sup> In mammals, concentrations of plasma phytosterol are low because of their poor absorption from the intestine and their faster excretion from liver, and metabolism to bile acids, compared with cholesterol.<sup>29</sup>

### Phenolic Constituents

The most important dietary phenolics are the phenolic acids (including hydroxybenzoic and hydroxycinnamic acids), polyphenols (hydrolyzable and condensed tannins) and flavonoids, the latter being the most studied group.<sup>31</sup> Phenols protect plants from oxidative damage. They have also been studied extensively as antioxidant protectants for humans. Haslam<sup>1</sup> points to current interest in the potential for amelioration of diseases simply by improving the dietary intake of nutrients with antioxidant properties, such as vitamin E, vitamin C,  $\beta$ -carotene and carotenoids, and plant phenolics, such as tannins and flavonoids. The food industry is faced with a challenge to include antioxidative phytochemicals in foods. Andlauer and Furst<sup>32</sup> addressed this challenge, especially in relation to cereals and wholegrain products. Anderson and Hanna<sup>33</sup> cited several observational studies that indicate a beneficial role for wholegrain intake in reducing the risk of coronary heart disease,<sup>34</sup> diabetes,<sup>35</sup> hypertension<sup>36</sup> and some types of cancer.<sup>37</sup> However, as Anderson and Hanna<sup>33</sup> pointed out, 'Longterm clinical trials with specific foods have not been done; therefore, this evidence is not available.'

The widespread interest in the potential benefits of phytochemicals as phenolic antioxidants has led to considerable commercialization activities surrounding several commodity extracts. An example of such well-studied free radical scavenger phytochemical mixtures has been commercialized as Pycnogenol<sup>®</sup> (procyanidin extracted from *Pinus maritima*), a complex combination of phenolic and polyphenolic compounds. Pycnogenol<sup>®</sup> exhibited low toxicity and no mutagenic activity in Ames tests, micro-nucleus assay in mouse bone marrow cells or in chromosome aberration assay in human lymphocytes *in vitro*.<sup>38</sup>

The effects of Pycnogenol<sup>®</sup> were tested in SAMP8 mice, a strain that is prone to senility. After feeding pycnogenol to SAMP8 mice for 2 months, their T- and B-cell function was significantly improved, and the proliferative capacity of haemopoietic progenitors of bone marrow was augmented. These results suggested the potential use of Pycnogenol<sup>®</sup> for either retardation or restoration of ageing deficits.<sup>39</sup>

### Flavonoids

The flavonoid subclasses of phenols include the minor flavonoids (flavanones and dihydroflavonols), flavones and flavonols. Nutritional studies of flavonoids in grapes<sup>40</sup> and wine,<sup>41</sup> and studies of flavonoids in medicinal plants<sup>42</sup> were reviewed recently. Among the

biological activities of flavonoids are actions against free radicals, free radical mediated cellular signaling, inflammation, allergies, platelet aggregation, microbes, ulcers, viruses and tumors and hepatotoxins.<sup>43</sup> Mechanisms by which flavonoids have been proposed to provide health benefits in addition to being direct chemical protectants involve modulatory effects on a variety of metabolic and signaling enzymes. Flavonoids have been shown to block the angiotensin-converting enzyme that raises blood pressure; they inhibit cyclooxygenase, which forms prostaglandins; and they block enzymes that produce estrogen. The implications of these *in vitro* inhibitory actions are that certain flavonoids could prevent platelet aggregation, reducing heart disease and thrombosis; and inhibit estrogen synthase, which binds estrogen to receptors in several tissues, thus decreasing the risk of estrogen-related cancers.

Hertog *et al*<sup>23</sup> quantitated the flavonoids quercetin, kaempferol, myricetin, apigenin and luteolin in various foods. In 1985, they assessed the flavonoid intake of 805 men aged 65–84 years. The baseline flavonoid intake averaged 25.9 mg daily. The major sources of intake were tea (61%), onions (13%) and apples (10%). Between 1985 and 1990, 43 of the study subjects died of coronary heart disease. The inverse association between flavonoid intake (analyzed in tertiles) and coronary heart disease mortality was significant. The relative risk of coronary heart disease mortality in the highest versus the lowest tertile of flavonoid intake was 0.42% (95% CI 0.20–0.88). Flavonoids in regularly consumed foods appeared to reduce the risk of death from coronary heart disease for the elderly men studied.

Whereas flavonoid intake has been associated with reduced risk from death from coronary heart disease,<sup>23</sup> some flavonoids have been reported to be mutagenic. Among the flavonoids quantitated by Hertog *et al*,<sup>23</sup> apigenin and luteolin, both flavones, are not mutagenic. In fact, luteolin is anti-mutagenic.<sup>44</sup> Luteolin also has anti-inflammatory and antibacterial activities.<sup>11</sup> Apigenin suppressed 12-O-tetradecanoylphorbol-1,3-acetate (TPA)-mediated tumor promotion of mouse skin, as did curcumin, a dietary pigmented polyphenol, possibly through suppression of protein kinase C activity and nuclear oncogene expression.<sup>45</sup> Apigenin is antibacterial, anti-inflammatory, diuretic, hypotensive, and also promotes smooth muscle relaxation.<sup>11</sup> Myricetin, a hexahydroxyflavone, exhibits antibacterial activity and has anti-gonadotropic activity, but apparently is not a mutagen.<sup>11</sup>

The flavonol kaempferol, which is widely found in the diet, has anti-inflammatory and antibacterial activities and is directly mutagenic.<sup>11</sup> For example, in short-term tests, such as the induction of chromosomal aberrations in eukaryotic cells, Silva *et al*<sup>46</sup> found a time-dependent biotransformation of kaempferol to quercetin, by cytochromes P450 in V79 cells. Quercetin, the most common flavonoid in higher plants, seems to contribute to the mutagenicity of

kaempferol in the presence of microsomal metabolizing systems. Quercetin inhibits a number of enzymes, inhibits smooth muscle contraction and proliferation of rat lymphocytes. Although it is anti-inflammatory, antibacterial, antiviral and anti-hepatotoxic, it exhibits mutagenic activity and allergenic properties.<sup>11</sup>

#### *Catechins, and gallic acids*

Major sources of catechins are grapes, berries, cocoa and green tea. Tea contains considerable amounts of gallic acid esters, such as epicatechin, epicatechin gallate and epigallocatechin gallate. Numerous studies have suggested that these components provide protective benefits by their free radical scavenging ability<sup>47</sup> and their inhibition of eicosanoid synthesis<sup>48</sup> and platelet aggregation.<sup>49</sup> On the basis of experimental evidence in cell culture systems and in animal models, as well as epidemiological evidence, Gupta *et al*<sup>50</sup> support the possible use of tea, especially green tea, for prevention of prostate cancer. However, Hollman *et al*<sup>51</sup> regard the question of flavonol protection against cardiovascular disease and cancer as remaining open.

In wines, catechins and procyanidins are involved in the astringency sensation.<sup>52</sup> Catechin is one of the major phenolics in grapes and red wines, and it is considered to be responsible for part of the protective effect of red wine against atherosclerotic cardiovascular disease.<sup>43,53,54</sup> Whereas little data have been produced to address the absorption and bioavailability of most polyphenolics, data on catechin from grapes and red wine are emerging. The absorption of catechin from wine has been studied. Donovan *et al*<sup>55</sup> measured catechin and catechin metabolites in plasma of human subjects following consumption of both alcoholized and dealcoholized red wine. Sulfate and sulfate-glucuronide conjugates, but little free catechin, were present. The metabolites/conjugates of catechin were eliminated from blood with a half-time of approximately 4h. These data confirmed that the grape polyphenolic flavonoid catechin is well absorbed, but rapidly metabolized and conjugated. The results suggest that the physiological properties of the metabolites in blood and tissues may be more important than the parent compounds found in the plants.

#### *Isoflavonoids*

Isoflavonoids are another subclass of the phenolic phytonutrients. Soybeans are an unusually concentrated source of isoflavones, including genistein and daidzein, and soy is the major source of dietary isoflavones. The isoflavones of soy have received considerable attention owing to their binding to the estrogen receptor class of compounds, thus representing an activity of a number of phytochemicals termed phytoestrogens. Genistein inhibits the growth of most hormone-dependent and independent cancer cells *in vitro*, including colonic cancer cells. Isoflavones have received considerable attention as potentially prevent-

ing and treating cancer and osteoporosis.<sup>56</sup> In mice, dietary soybean components inhibited the growth of experimental prostate cancer and altered tumor biomarkers associated with angiogenesis.<sup>57</sup> Unfortunately, convincing intervention studies have not been reported: although epidemiological data suggest that soy potentially decreases the risk of breast cancer and prostate cancer, the evidence that soy exerts a protective effect against colonic cancer is limited.<sup>58</sup> Exciting mechanistic results that emerged recently showed that the isoflavone genistein from soy selectively bound the beta-estrogen receptor and reduced binding to the alpha-receptor 20-fold.<sup>59</sup> This would argue for isoflavones providing significant cardioprotective effects without adversely affecting cancer risk of reproductive tissues.

#### *Anthocyanidins*

Anthocyanidins are water-soluble flavonoids that are aglycones of anthocyanins. Haslam<sup>1</sup> cited the principal naturally occurring anthocyanidins as pelargonidin, cyanidin, paeonidin, delphinidin, petunidin and malvidin. These compounds are among the principal pigments in fruits and flowers. The color of these pigments is influenced by pH and metal ion complexes. Like other flavonoids, anthocyanidins are antioxidants *in vitro*,<sup>60,61</sup> and might be expected to have antioxidative and anti-mutagenic properties *in vivo*. Although Pool *et al*<sup>61</sup> found potent antioxidant activity for isolated anthocyanidins (aglycons and glycosides) and complex plant samples in the ferric-reducing ability assay, these compounds did not prevent hydrogen peroxide-induced oxidation of DNA bases in HT29 clone 19A cells. The investigators raised the question as to whether anthocyanidins have anti-cancer potential within specific tissues.

#### **Alkaloids and other nitrogen-containing metabolites**

##### *Glucosinolates*

Glucosinolates, which are present in cruciferous vegetables, are activators of liver detoxification enzymes. Consumption of cruciferous vegetables offers a phytochemical strategy for providing protection against carcinogenesis, mutagenesis and other forms of toxicity of electrophiles and reactive forms of oxygen.<sup>62</sup> The general importance of the condition of plants to their phytochemical content is illustrated by the specific example that three-day-old sprouts of cultivars of certain crucifers, including broccoli and cauliflower, contain 10–100 times more glucoraphanin (the glucosinolate of sulforaphane) than do the corresponding mature plants. Crucifer sprouts may protect against the risk of cancer more effectively than the same quantity of mature vegetables of the same variety.<sup>62</sup>

Glucosinolates are transformed into isothiocyanates, dithiolsiones and sulforaphane. Glucosinolates are released from damaged plant cells and converted by the enzyme myrosinase into isothiocyanates, some of which inhibit the neoplastic effects of various

carcinogens at a number of organ sites. The mechanism of the protective effects is thought to involve the modulation of carcinogen metabolism by the induction of Phase 2 detoxification enzymes and inhibition of Phase 1 carcinogen-activating enzymes,<sup>63</sup> thereby possibly influencing several processes related to chemical carcinogenesis, eg the metabolism, DNA binding and mutagenic activity of promutagens. A reducing effect on tumor formation has been shown in rats and mice, and studies carried out in humans using high but realistic human consumption amounts of indoles and brassica vegetables have shown putative positive effects on health. Shapiro *et al*<sup>64</sup> examined the fate of ingested isothiocyanates and glucosinolates in humans by quantifying isothiocyanates and their urinary metabolites (largely dithiocarbamates). They established that humans convert substantial amounts of isothiocyanates and glucosinolates to urinary dithiocarbamates, thus paving the way for meaningful studies of Phase 2 enzyme induction in humans.

#### Indoles

As reviewed by Telang *et al*,<sup>65</sup> indole-3-carbinol is a glucosinolate metabolite that inhibits organ-site carcinogenesis in rodent models. These investigators tested the effects of this compound on reduction of mammary-derived 184B5 cells initiated with a chemical carcinogen or with an oncogene, and on mammary carcinoma-derived MDA-MD231 cells to determine whether it inhibits aberrant proliferation in initiated and transformed cells. They also studied whether inhibition of aberrant proliferation was associated with altered cell cycle progression, estradiol metabolism and apoptosis. From their results, they suggested that the observed preventive efficacy of indole-3-carbinol on human mammary carcinogenesis may be due in part to its ability to regulate cell cycle progression, increase the formation of anti-proliferative estradiol metabolite and induce cellular apoptosis.

Long-term use of an estrogen preparation that is not accompanied by progestogen is associated with a large increase in the risk of endometrial cancer in postmenopausal women.<sup>66,67</sup> However, the occurrence of other gynecological cancers appears not to be associated with the use of unopposed estrogens.<sup>66</sup> Because of the significant cervical cancer risk associated with human papilloma virus infection, compounds that interfere with the activity of products of this virus may be effective chemopreventives.<sup>67</sup> In cervical cancer cells, estradiol increased the expression of human papilloma virus oncogenes, whereas indole-3-carbinol abrogated the estrogen-increased expression of the oncogenes.<sup>68,69</sup> It has been reported that indole-3-carbinol increased the expression of cytochrome P450 enzymes that are responsible for the 2-hydroxylation of estrogen, resulting in the anti-estrogenic activity. A clinical intervention study with obese premenopausal women involved their ingestion of 400 mg of purified indole-3-carbinol daily for 2 months.<sup>70</sup> The subjects experienced increased estrogen 2-hydroxylation. The

response may indicate that indole-3-carbinol helps reduce estrogen-dependent cancer risk.

#### Fiber

Whereas dietary meat and fat intake have a positive relation to the incidence of colon cancer, dietary fiber has been associated with alterations of the colonic environment that protect against colorectal diseases. Among the theories on colonic carcinogenesis are those that involve increased concentrations of bile acids and their metabolites, alterations in colonic pH, low  $\text{Ca}^{2+}$ , elevated  $\text{NH}_3$  and long-chain fatty acid concentrations, and alterations in bacterial profiles. Fiber may also provide protection by increasing fecal bulk, which dilutes the increased colonic bile acid concentrations that occur with a high-fat diet.<sup>71</sup> Short-chain fatty acids, including butyric acid, and dietary sugar beet fiber also suppress cholesterol synthesis in a rat liver and intestine model.<sup>72</sup>

Reviews by Smith and German<sup>73</sup> and Smith *et al*<sup>74</sup> point out that different dietary fibers have markedly different cancer protective effects, and that the differences may be related to the differential bacterial fermentation of fiber in the colon to short-chain fatty acids, especially butyric acid. Butyric acid induces growth arrest, differentiation and apoptosis of colonic epithelial cells and tumor cells *in vitro*. Butyric acid in the colon also appears to influence the ongoing process of apoptosis within the mucosa. The potential for fermentation of fiber to butyric acid and its derivatives is of considerable interest. Butyric acid has a short half-life *in vivo*; however, its enrichment through food products, such as fiber and starch, may emerge as a molecular-based strategy that provides significant health benefits.

#### PHYTOCHEMICALS AND TREATMENT OF SPECIFIC CONDITIONS OR DISEASES

The basis for the use of therapeutic drugs in modern-day medicine is the history of natural product use in ancient times and in folk medicine around the world. Primitive cultures used plants as a source not only of medicines but also of toxic substances for killing animals, and for stimulants and hallucinogens used in religious rites. Traditionally, natural plant products have been the source for the search for new drugs, by pharmaceutical companies. Plant sources of herbal medicines rich in polyphenols are being studied in detail to find active molecules with healing properties. Haslam<sup>1</sup> itemized some of the medicinal plants that contain polyphenolic metabolites and the disorders for which they have been used historically: tree peony—used to cure disorders of the bloodstream, such as high blood pressure; bearberry—used as a diuretic and in disorders of the bladder and urinary tract; agrimony—used as a digestive system astringent, diuretic and hemostatic agent; geranii herba—used as an astringent, anti-hemorrhagic and anti-inflammatory agent; meadowsweet—used as a mild astringent, anti-rheu-

matic anti-inflammatory agent and as a diuretic; raspberry—used in digestive system disorders; hawthorn—used as digestive system astringent, diuretic and as a cardiac tonic to treat high blood pressure; and rose bay willow herb—used as an intestinal astringent, anti-spasmodic in whooping cough and asthma, and in ointments to treat cutaneous infections.

### Ethnobotanicals

One example of the extensive amount of information currently available to the public is the United States Department of Agriculture (USDA) Agricultural Research Service (ARS) website of extensive databases for phytochemicals and ethnobotanicals (<http://www.ars-grin.gov/duke/>); this webpage is called 'Dr. Duke's Phytochemical and Ethnobotanical Databases.' The databases are divided and subdivided into the following: plant searches (chemicals and activities in a particular plant; high concentration chemicals; chemicals with one activity; ethnobotanical uses); chemical searches (plants with a chosen chemical; activities of a chosen chemical); activity searches (plants with a specific activity; search for plants with several activities; chemicals with a specific activity; chemicals with a lethal dose value); and ethnobotany searches (ethnobotanical uses for a particular plant; plants with a particular ethnobotanical use).

Several tests of medicinal efficacy of phytochemicals in ethnobotanicals from various indigenous cultures have been reported. Hammond *et al*<sup>75</sup> studied 33 species of medicinal plants from north-eastern Peru. Tona *et al*<sup>76</sup> reported studies of 45 Congolese plant extracts used to treat diarrhea in traditional medicine. Halberstein<sup>77</sup> made a descriptive survey of 18 medicinal plants on Grand Caicos Island in the West Indies. The phytochemical constituents in the plants suggest pharmacological and/or physiological efficacy in the ethnomedical treatment of various disorders. Traditional procedures to prepare the plant preparations may enhance the chemotherapeutic value of the plant derivatives, while at the same time reducing their potential toxicity. Kenyan medicinal plants were extracted and tested for *in vitro* anti-plasmodial active against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. Out of 16 extracts, 12 were active against the resistant strains and seven were active against the sensitive strain.<sup>78</sup> Freiburghaus *et al*<sup>79</sup> studied nine plant species from Tanzania and Uganda that are used by traditional healers for the treatment of human African trypanosomiasis (sleeping sickness). Their *in vitro* activity against *Trypanosoma brucei rhodesiense* was tested. The results confirmed the potential of ethnobotanically-selected plants as remedies against sleeping sickness. Extracts of 23 plants used as anti-spasmodics in the traditional medicine of the United Arab Emirates were tested for their effects on intestinal smooth muscle activity.<sup>80</sup> Some plants, especially *Rhazya stricta*, exhibited anti-spasmodic activity, indicating its potential use in anti-spasmodic medication.

### Phytochemicals in clinical applications, animal studies, cells in culture or *in vitro*

Lacking from the information available to the food and drug industries is laboratory and clinical evidence that lends support to specific health claims. Most studies are of the observational and descriptive type, whereas information on functions and mechanisms of action are sparse. The following sections cite recent research evidence for the beneficial effects of isolated phytochemicals or of plant extracts against a variety of disease conditions. The biological test systems include humans, animal models and *in vitro* cultured cell systems. Where mechanisms of action have been determined, or mechanisms have been hypothesized, this information is also presented. A distinction must be drawn between the types of information that can be obtained from *in vitro* studies, animal studies and clinical studies with humans. Any reference to effectiveness of phytochemical nutraceuticals against disease states can only be drawn from carefully controlled human studies. Studies with animal models yield results relevant only to the specific animal model tested, although inferences to phytochemical effects in animals are often extrapolated by the investigators to their potential effects on diseases or health conditions in humans. Studies limited strictly to testing of the behavior of molecules or the interactions of molecules *in vitro* or in cell culture are necessary to provide badly needed information on mechanisms of action of the molecules. However, results obtained by such studies cannot be used as evidence to make claims for their effectiveness against disease states in any intact organism. Even in clinical studies, effects of nutrients are usually confounded by the interactions of molecules in the body.

Many types of interactions between drugs and nutrients are known.<sup>81</sup> When the *in vivo* effect of consuming a single nutrient molecule at a time or a combination of molecules is tested, the results can lead to unexpected or incomplete information. One such case is the study reported by Omenn *et al*<sup>82</sup> in which  $\beta$ -carotene was tested for chemopreventive effects against cancer: this nutrient increased cancer rates in smokers. This observation has been interpreted as the result of the actions of carotenes or their oxidation product retinoids in promoting cell proliferation in the presence of smoke-related molecules.<sup>83</sup> Interactions also can occur between nutrients provided in the same food source or provided as nutritional supplements. For example, Kubena and McMurray<sup>84</sup> pointed out that, 'Availability of one nutrient may impair or enhance the action of another in the immune system, as reported for nutrients such as vitamin E and selenium, vitamin E and vitamin A, zinc and copper, and dietary fatty acids and vitamin A.' Moreover, calcium can interfere with leukocyte function by displacing magnesium ions needed for cell adhesion.<sup>85</sup>

Another interesting interaction of dietary nutrients is the decrease in fat and protein digestibility when fiber intake is increased.<sup>86</sup> As a result of the decreased

digestibility, the metabolizable energy content of the diet decreases as fiber intake increases.

Results that illustrate a strong interaction between diet and specific phytochemicals have been interpreted, or at least argued, to indicate that the role of phytochemicals in health is minimal and that their potential for successful intervention in human health is overstated. The opposite is true. The fact that dietary components and phytochemicals interact simply means that there are opportunities to complement phytochemicals with diet in order to maximize their actions. However, the complexity of these relations means that the precise mechanisms of actions must be understood so that complementary strategies can be developed with sound molecular rationales.

#### **In vitro testing of anti-psychotic phytochemicals**

Chung *et al*<sup>87</sup> developed assays to screen the phytochemical and pharmacological profiles of natural products used in Korean traditional medicine to treat psychotic illnesses. Among the 31 plants screened were *Gardenia jasminoides*, *Citrus unshiu*, *Citrus aurantium*, *Chrysanthemum indicum*, *Ginseng radix* and *Liriope koreana*. In screening assays, some of the plant products exhibited potent selectivity to receptors such as monoamine receptors that are assumed to be involved in mental disorders. These investigators focused their research on ingredients in plant extracts that have central nervous system effects, with the hope of future development of new psychotropic drugs that do not have the serious side-effects often associated with modern psychopharmacological drugs.

#### **Analgesic and anti-inflammatory effects in animals**

The analgesic properties of phytochemical constituents isolated from a methanolic extract of *Sebastiania schottiana* roots were tested with mice by intraperitoneal route in an acetic acid-induced abdominal constriction model.<sup>88</sup> The compounds isolated were moretenone, glutinol,  $\beta$ -sitosterol and stigmasterol. Glutinol and moretenone exhibited marked analgesic action, being 16- to 26-fold higher in efficacy than aspirin or paracetamol. The authors suggested that the analgesic compounds in *S schottiana* justify, at least partially, the popular use of this plant for the treatment of urinary problems.

The flavone titonine (7,4'-dimethoxy-3'-hydroxy-flavone), isolated from the leaves of *Viola michelli* Heckel (Myristicaceae), was methylated and acetylated;<sup>89</sup> the native compound and the methylated and acetylated compounds were evaluated for anti-inflammatory activity 30 min following intraperitoneal injection of 10 mg kg<sup>-1</sup> in rats using the paw edema test with carrageenin. The compounds were 22, 41 and 68% inhibitory, respectively. The analgesic test using the writhing test method showed a dose-dependent response.

A hexane extract of *Eryngium foetidum* L (Apiaceae), a Caribbean endemic plant used in folk medicine for treatment of several anti-inflammatory disorders, was

chromatographically fractionated.<sup>90</sup> The extract contained a number of terpenoid compounds. The topical anti-inflammatory activity of the hexane extract was evaluated in the mouse by auricular edema induced by 12-*O*-tetradecanoylphorbol acetate. In both a chronic and acute model, oedema was reduced. The identity of the active ingredient(s) was not determined, although more than one bioactive component was probably involved in the anti-inflammatory activity.

Other studies have reported the anti-inflammatory activity of *Lobelia laxiflora* against carageenan and cobra venom-induced acute inflammation in mice.<sup>91</sup> Based on *in vitro* studies with fractions of various plant extracts, the investigators hypothesized that the anti-inflammatory mechanism involved the inhibition of complement activation.

Species of the Spanish endemic *Teucrium buxifolium*, traditionally used for treatment of rheumatic and other inflammatory disorders, contained potent anti-inflammatory agents against experimentally-induced arthritis and carrageenin paw edema. *Teucrium buxifolium* species also displayed significant anti-ulcer and cytoprotective activity.<sup>92</sup>

Latha *et al*<sup>93</sup> tested the anti-arthritis effects of administering 100 mg of an alcoholic extract from the flower of *Vernonia cinerea* (Asteraceae; Less) per kg body weight to adjuvant arthritic rats. The major histopathological changes in the hindpaws of the rats were reversed, thus showing that anti-inflammatory compounds were among the alkaloids, saponins, steroids and flavonoids in the extract.

#### **Antibacterial, antiparasitic and antiviral effects**

A water extract of the Bulgarian medicinal plant, *Geranium sanguineum* L (Geraniaceae), significantly inhibited the replication of herpes simplex virus Type 1 and Type 2 as shown by the reduction of virus-induced cytopathogenic effect and protection of cells.<sup>94</sup> In preliminary experiments, the extract delayed the development of herpetic vesicles following infection with HSV1 in albino guinea pigs. No mechanism of action was reported, but the inhibitory effect on virus replication was reported to be related to the content of polyphenol compounds (flavonoids, catechins, a polyphenolic acid and condensed tannins).

Two isoprenylflavones present in methanolic extracts from *Artocarpus heterophyllus* showed intensive activity as antibacterial and cariogenic plaque-forming streptococci.<sup>95</sup> Among 13 flavanones tested in one study, tetrahydroxyflavanones from *Sophora exigua* and *Echinosophora koreensis* actively inhibited the growth of methicillin-resistant *Staphylococcus aureus*.<sup>96</sup>

#### **Cancer**

##### *Anti-mutagenic testing*

Ito *et al*<sup>97</sup> isolated and identified ten phytochemicals from seeds of the *Casimiroa edulis* Llave *et* Lex (Rutaceae) tree, which grows in Mexico and Central America. This tree produces edible fruits known as zapote blanco. The ethyl acetate extract from these

seeds inhibited mutagenicity induced by 7,12-dimethylbenz[1]anthracene with *Salmonella typhimurium* strain TM677. The extract completely inhibited DMBA-induced preneoplastic lesions in vitro in mouse mammary gland organ culture.

#### *Cell culture studies of promyelocytic leukemia cells*

Resveratrol is a triphenolic stilbene present in grapes and other plants. The antioxidant and anti-inflammatory activities of resveratrol have been hypothesized to be responsible for the beneficial effects of red wine on coronary heart disease. However, the molecular mechanisms that underlie anti-tumourigenic or chemopreventive activities are unknown. Surh *et al*<sup>98</sup> reported that resveratrol inhibits growth and has anti-proliferative properties in cultured human promyelocytic leukemia (HL60) cells. These effects appear to be related to the induction of apoptotic cell death by resveratrol, as determined by morphological and ultrastructural changes and other indices. Thus, this phytochemical may be protective against coronary heart disease and also have cancer therapeutic activity. Gehm *et al*<sup>99</sup> reported that resveratrol increased the expression of native estrogen-regulated genes, and stimulated the proliferation of estrogen-dependent T47D breast cells. Gehm *et al*<sup>99</sup> and also Calabrese<sup>100</sup> concluded that resveratrol is a phytoestrogen receptor agonist, and suggested that this finding may be relevant to the reported cardiovascular benefits of drinking wine. However, the concentrations of resveratrol necessary to elicit these effects in vitro may be unachievable *in vivo* by consuming natural commodities, even those extremely rich in resveratrol.

Pure soy isoflavones (genistein, genistin, daidzein and biochanin A) and a soy phytochemical concentrate exhibited dose-dependent growth inhibition of murine (MB49 and MBT2) and human (HT1376, UMUC3, RT4, J82 and TCCSUP) bladder cancer cell lines, with the degree of inhibition depending on the cell line.<sup>101</sup> Soy isoflavones induced a G1M cell cycle arrest in all human and murine lines evaluated by flow cytometry. Some cancer lines exhibited DNA fragmentation consistent with apoptosis.

#### *Animal and human studies*

Surh *et al*<sup>102</sup> reviewed evidence from animal studies to support the anti-carcinogenic and anti-mutagenic effects of capsaicin, the pungent ingredient present in red pepper and ginger. In humans, curcumin, another polyphenolic phytochemical, is under preclinical trial evaluation as an anti-inflammatory and cancer preventive drug.<sup>103</sup>

As evaluated by several biomarkers in tumor tissue, soy products decreased angiogenesis, increased apoptosis and slightly decreased proliferation of MB49 bladder carcinoma cells injected into mice.<sup>84,101</sup> Tumour volumes from mice treated with genistein, dietary soy phytochemical concentrate at 1%, or dietary soy protein isolate were decreased 40, 48 or 37%, respectively, compared with controls. The cell

culture studies cited above and the animal studies cited here suggest the need for further investigations of the use of soy products in bladder cancer prevention and treatment programs or as anti-angiogenic agents.

Genistein (5,7,4'-trihydroxyisoflavone) is one of two major isoflavonoids in soy. In human breast cancer cells in culture, genistein has anti-proliferative effects on mitogen-stimulated growth. Soy isoflavonoid conjugates have chemopreventive activity in carcinogen-induced rat models of breast cancer.<sup>104</sup> In rats, the mechanism of the preventive action is in part dependent on its estrogenic activity, which causes rapid differentiation of cells of the mammary gland. The authors point to the importance of future studies to examine the interaction of soy isoflavonoids with other phytochemical components and to test effects in newly developed animal models of breast cancer in which specific genes have been activated or inactivated. As it is important to remember that food phytochemicals are not consumed in isolated, purified form, but in combination with other phytochemicals and food components, this type of approach should apply to studies of the health benefit effects of all food phytochemicals.

#### **REGULATORY ASPECTS OF NUTRACEUTICALS**

The rapid growth of so-called health foods, now frequently defined by this industry as nutraceuticals, led to passage of the Nutrition Labeling and Education Act of 1990 and the Dietary Supplement Health and Education Act of 1994. These acts have impacted the information available to consumers who now are expending billions of dollars each year for the purchase of health-related foods and supplements. Clydesdale<sup>105</sup> aptly proposed the establishment of scientific criteria for health claims for functional foods, especially in relation to the increasing global economy. Consumers, government, industry and academia all need to be involved in an international understanding, based on science and ethics, for health claims for functional foods, including those of phytochemical origin.

#### **PHYTOCHEMICALS: FUTURE PROSPECTS**

Although the use of plants for medicinal uses by indigenous people of many continents has a long history, only recently has scientifically supported nutritional and medical evidence allowed phytonutrients to emerge as being potentially generally effective. The 'new' nutraceuticals of plant origin may evolve to be considered a vital aspect of dietary disease-preventive food components. Not many years ago, the National Institutes of Health did not support research that focused on dietary means to solve health problems. Noteworthy is the recent establishment of Centers for the study of alternative medicine. Careful studies are being done on the various phytonutrients for their roles in the prevention of chronic degenerative

diseases. The resurgence of interest in these compounds will eventually lead to needed information on structure-function relationships. The individual studies cited above, as well as a plethora of texts reviewing the current state of the field (eg see Bidlack *et al*<sup>106</sup>), are evidence that this research-intensive process has already begun. Basic to obtaining this information will be the development of the tools to isolate and identify the thousands of bioactive components of plants.

The potential growth of the food industry into the realm of health-promoting ingredients for food products was emphasized at the Institute of Food Technologists' annual meeting in Atlanta, GA, USA in 1998 and in 1999. In 1998, issues arising during the application of nutraceutical ingredients into food products were discussed in a symposium, 'Developing Nutraceuticals of the New Millennium,' and in 1999, again there was an emphasis on nutraceuticals and functional foods, with the 'Hot Topic' being 'The Food Medicine Show: from Snake Oil to Fish Oil,' and with symposia such as 'Nutraceutical/Functional Foods: Processing, Product Development, and Regulation,' covering various aspects of the concern and interest of the food industry.

One example of regulatory changes in the USA that is of interest to manufacturers is that resulting from the Dietary Supplement and Health Education Act of 1994. The Dietary Supplement Health Education Act of 1994 is an amendment to the Food, Drug and Cosmetic Act. This Act removes dietary supplements from the labeling provisions of the Nutrition Labeling and Health Education Act. However, the manufacturer must have substantiation that the label is truthful and not misleading (but there is no indication that this information has to be provided to the FDA). The following information must also be prominently displayed, 'This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.' The debate over nutritional labeling of dietary supplements continues.

One challenge remaining is that of educating the public to make wise choices in foods that are consumed. The food marketplace is increasingly varied, with individual free choice being the single most important driving force. Now it can truly be said that individual consumers eat what they choose. The food industry can play a significant role in improving the nutritional density deriving from the food consumption habits of the public. The ever-widening choice of food ingredients makes it possible for food designers to provide food choices that meet the public's expressed desire for healthy food and at the same time to provide what the public really wants: good tasting foods that also provide true nutritional value. Other aspects of determining the role of phytochemicals in functional foods include consumer attitudes, any competitive advantage for manufacturers producing functional foods and identification of those areas of research needed to produce foods with

the desired health effects.<sup>107</sup> Reid<sup>108</sup> itemized the following issues that face the food processing industry when 'nutritional ingredients' are fortified in foods: 'nutritional activity in a finished product, flavors and color problems, solubility and secondary effects on functionality.' Other issues faced by the food industry include safety, regulations imposed by various governments and health claims.<sup>109</sup>

Childs and Poryzees<sup>110</sup> addressed an issue of great interest to future developments in the marketing of nutraceuticals: consumer attitudes and public policy implications. Marketing of nutraceuticals and functional foods, whether of plant or animal origin, will be to a large extent determined by surveys such as carried out by these investigators. In the USA, a national survey showed that 55% of the population believed in disease-preventive properties of natural foods. The term most preferred to describe the nutraceutical category was nutritional foods (63% of respondents), followed by medical food (8%) and functional foods (5%).

Several reviews have addressed the future of markets for nutraceuticals in the USA, Japan and Europe,<sup>111</sup> Europe (pharmaceutical and food opportunities)<sup>112</sup> and Asia (Japan and China).<sup>113</sup> Shukla<sup>114</sup> reviewed commercial developments in nutraceuticals in terms of patents for anti-carcinogenic foods, anti-diabetogenic foods, cerebro-active foods, prebiotic oligosaccharides and *Bifidobacterium* probiotic foods, and foods for prevention of osteoporosis and rheumatoid arthritis. In 1997, Aarts<sup>115</sup> estimated that the \$50–60 million per year medical foods sector in the USA was growing at the rate of 25% per year. Gilmore<sup>116</sup> reported that the US nutraceutical industry had a market value of \$11 billion, and that it was growing at an average annual rate of 12%. Obviously, the value of the global nutraceutical market is significant. In the same year, Murphy<sup>117</sup> estimated that one in three Americans uses some form of alternative or complementary/adjunct therapy. Food processing companies are now considering the marketing advantages of exploiting recent studies showing the health benefits of phytochemicals in common foods.<sup>118</sup>

The choice of healthy ingredients not traditionally considered as nutrients (ie protein, fat and carbohydrate nutrients) extends beyond the plant world. This review focuses briefly on examples of recent research on specific phytonutrients as they may relate to specific diseases. The review has not included information on the world of beneficial nutrients and health-promoting components that are provided, for example, in dairy products or that can be enhanced through processing of dairy products. The future of nutraceuticals of both plant and animal origin holds exciting opportunities for the food industry to create novel food products. The food industry will need to convince investors of the potential for monetary rewards to be gained by investing in the value of nutraceuticals, and it will need to market the products so as to capture the interest of and, perhaps most important, to please the tastes of consumers.

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