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Health-related Interactions of Phytochemicals

Mary Ann Lila and Ilya Raskin

ABSTRACT: Interactions between phytochemical components often modify the pharmacological effects of botanical dietary supplements, functional foods, or drugs. These interactions can either potentiate the effect of bioactive phytochemicals or interfere with their activity. This review defines and explores 2 types of phytochemical interactions: endointeractions that occur between components within a plant species and exointeractions that occur between components from different plants or between plants and synthetic drugs. Exointeractions and endointeractions between and within the complex mixtures of phytochemicals may have a profound effect on human health. Few well-characterized interactions were shown to affect a wide range of biological processes such as metabolism, bioavailability, solubility, cellular uptake and efflux, and body clearance. Phytochemical interactions may explain the health effects of regional diets, undesirable side effects of drugs, and inconsistent performance of dietary supplements. Better understanding of health-related phytochemical interactions should lead to a more sophisticated, holistic approach to disease prevention and treatment.
Keywords: phytochemicals, chemical interactions, human health, food, drugs

Introduction

The 20th century will always be remembered for major triumphs in the human struggle against diseases. These triumphs included the development of the pharmaceutical industry, which turned advances in organic chemistry into a formidable arsenal of drugs mainly based on synthetic organic molecules. Early successes in discovery of these molecules were due to a powerful reductionism approach that began with identification of biologically active mixtures of natural products produced by bacteria, fungi, and plants, and subsequent isolation of the main active ingredient. The isolated active ingredient was then either manufactured directly from the source organism, synthesized de novo, or chemically modified to improve safety or efficacy. This approach was particularly effective for anti-infectives, antineoplastic, analgesic, anticholinergic, cardiovascular, and muscle relaxant indications. Penicillin, streptomycin, taxol, vinblastine, vincristine, opiates, reserpine, digitoxin, and tubocurarine saved or extended billions of lives either directly or by facilitating complex surgical procedures. The latter part of the 20th century added many non-natural product-based approaches to sourcing bioactive molecules, such as structure-activity guided synthesis, combinatorial chemistry, and computational design. Modern pharmaceutical products developed from natural and synthetic sources are usually called new chemical entities (NCEs) because they are based on single active ingredients approved by the United States Food and Drug Administration (USFDA) or similar regulatory agency in another country.

Human consumption of bioactive natural products is not limited to pharmaceutical products. A much greater number is ingested as foods or dietary supplements (nutraceuticals). While these are just as likely to exert biological effects that go far beyond providing cal-

ories and essential nutrients, the pharmacological properties of foods and dietary supplements are much more difficult to define and study. This is because the reductionism approach of modern pharmacology is not designed to study pleiotropic effects produced by complex mixtures of compounds. Defining these effects requires a much more sophisticated interactive matrix and multifarious parallel approaches that have not been easy to develop. The NCE paradigm often falls short of treating polygenic causes for many chronic diseases, requiring patients to swallow many pills at the same time, which have not been developed to work with each other. Historically, the pleiotropic approach to medicine was best articulated not by Western medicine but by traditional Chinese and Ayurvedic medicinal systems that emphasized the positive and negative interactions of different components in complex medicinal mixtures. However, because these systems lacked scientific validation and standardization, the modern medical community did not give them much credibility. The purpose of this review is to summarize the current state of knowledge about how interactions between components account for the pharmacological effects of plant-based functional foods, botanical drugs (multicomponent plant extracts approved as drugs by the USFDA), and dietary supplements. Specifically, this review discusses 2 types of molecular interactions: those that occur between components within a single medicinally-active plant species (endointeractions) and interactions that occur between components from different plants, or from plants and synthetic drugs, which may be ingested together (exointeractions).

Defining the Interactions

The vast array of phytochemicals has largely escaped structural and functional characterization, despite significant advances in analytical and screening technology (Mendelson and Balick 1995; Raskin and others 2002). While the functions of most secondary metabolites synthesized by plants are still obscure, a significant proportion are known to play roles in defense and signaling on the cellular and organismal levels. The effectiveness of this chemical

Table 1—Positive and negative endointeractions between compounds in complex mixtures[a]

Type of interaction	Examples
Positive interactions (potentiation)	Purified sulforaphane or intact glucosinolates and other broccoli compounds and upregulation of quinine reductase. Lycopene and other tomato phytochemicals and efficacy against prostate cancer. Polyphenolic compounds in cranberry and inhibition of human tumor cell lines.
Additive effects	Soluble and bound phenolics and fruit antioxidant capacity. Polyphenolic mixtures and inhibition of enzymatic activities in rat brain and liver.
Synergistic effects	Hyperforin and rutin from St. John's wort for antidepressant effect. Breakdown products from Brussels sprouts and up-regulation of Phase II detoxification enzymes.
Negative interactions (interferences)	Proanthocyanidins interference with caffeine in teas.

[a]All examples are referenced in the text.

arsenal may be because of a plant's use of interacting phytochemicals to accomplish many complementary tasks. Thus, it is not surprising that mixtures of plant secondary metabolites could be more biologically active than individual components.

Interactions between different compounds in complex mixtures can be positive or negative. Positive interactions that intensify the potency of a bioactive product are generally called *potentiation*. Additive and synergistic interactions are subsets of potentiation and are invoked when the potentiation is experimentally characterized and quantified. Additive effects occur when 2 or more compounds in a mixture interact to provide a combined effect that is equal to the sum of the effects of the individual components. *Synergies* refer to cases when combinations of bioactive substances exert effects that are greater than the sum of individual components. Typically, synergies indicate that the compounds in the mixture act via different mechanisms and/or on different disease-associated targets. The nature of these positive interactions must be demonstrated through reconstitution experiments in which the effects of interacting compounds are measured separately and in combination. In most other cases, no defined, measurable bioactivity or function can be assigned to some or all of the interacting phytochemical compounds. Yet, the combined bioactivity of the mixture is potentiated when the interaction results in improved solubility, absorption, safety, stability, or bioavailability of the active principle. Negative interactions (interferences) occur when certain components of the mixture inhibit full biological activity of pharmacologically-active compounds by reducing their stability or bioavailability or by enhancing their metabolism. Probably the larger portion of negative interactions between botanical foods, supplements, and drugs described to date are exointeractions, whereas the larger portion of characterized positive interactions are endointeractions.

It is possible that the evolutionary significance of a large number of phytochemicals present in each plant lies in their intricate mutually potentiating effects that provide protection against diverse pathogenic microbes and herbivores and ensure more reliable signaling to pollinators and other beneficial organisms. The same mechanisms and interactions between phytochemicals that aid the plant in its own life cycle can be equally valuable to the human or animal that consumes these compounds. It is more difficult to explain why plants have evolved so many compounds that interact with human therapeutic targets, assuming that chemical evolution and selection has played a role in this phenomenon. It is logical to argue that the antimicrobial and selectively cytotoxic compounds that protect plants against infectious diseases and herbivores assume similar protective roles as human anti-infective and antineoplastic therapeutics. In other cases, the pharmacological activities

of phytochemicals may be coincidental. Yet, most have evolved to play some function in biological systems and that should make them better therapeutic agents than randomly chosen synthetic chemicals. Modern medicine has only recently learned how rapidly pathogens and cancer cells can develop resistance to single ingredient drugs, necessitating the administration of complex drug cocktails to circumvent or delay the resistance. To survive, plants may have learned this strategy very early in their evolution. By relying on combinations of pleiotropic, multitargeted molecules, plants may have perfected interacting phytochemical complexes, which may be exploited by modern medicine during its gradual transition from single-ingredient drugs to multicomponent therapeutics.

Endointeractions

Endointeractions, as defined previously, happen between phytochemicals that are naturally co-occurring within edible plants and modify the pharmacological properties of the food or extract (Liu 2003). When interactions such as these are potentiating, the efficacy or potency of the biological activity is intensified.

Instances of potentiation or interference between co-occuring phytochemicals are generally well recognized and often cited but, with few exceptions, are seldom validated or quantified (Table 1). The following examples illustrate the breadth and diversity of phytochemical endointeractions that modulate biological activity in mammalian systems.

One of the best documented examples of endointeractions between bioactive phytochemicals concerns the bioactive carotenoid pigments in tomatoes. Lycopene, a red-pigmented carotenoid with antioxidant activity, has been repeatedly linked to lowered risk of prostate cancer in epidemiological studies supported by in vitro and in vivo experimentation. A series of comprehensive prostate cancer survival studies indicates that a combination of components from the tomato fruit confer cancer chemoprotective benefits. While lycopene is a factor involved in reducing the risk of prostate cancer, it is unclear whether lycopene *alone* is capable of providing any benefit toward reduced risk of prostate cancer (Gann and Khachik 2003).

Male rats treated with N-methyl-N-nitrosourea and testosterone to induce prostate cancer were randomly assigned to dietary regimes enhanced with either whole tomato powder or lycopene. Four weeks into the study, rats were further subdivided into groups allowed ad libitum feeding or a 20% restricted daily intake diet. Rats that consumed whole tomato product had a 26% lower risk of prostate cancer death as compared with control, whereas only minor protective benefits were found for the rats fed purified lycopene. The purity and integrity of the lycopene from all treatments in the AIN-93 diet were analyzed post-study, to ensure that purified lycopene (which was

protected in a beadlet matrix) was not merely more prone to oxidation than the lycopene delivered within the whole tomato product. Final levels of deterioration and isomerization were strictly monitored in all the treatment diets. Rats on the restricted intake diet had an even lower risk of developing prostate cancer (Boileau and others 2003). In vitro tests have provided further evidence suggesting that multiple tomato components, including other carotenoids and polyphenolics, potentiate lycopene action and confer chemopreventive activity (Campbell and others 2003). Zaripheh and others (2003) recently administered labeled lycopene to rats to elucidate its biodistribution and metabolism, and suggested that not only lycopene, but metabolites and isomers that accumulate in the prostate, interact in cancer chemoprevention. Other studies have demonstrated that mixtures of carotenoids or associations between carotenoids and other antioxidant phytochemicals increased biological activity (Paiva and Russell 1999). Beta-carotene, like lycopene, is apparently not chemoprotective when administered alone, especially at high levels; mixtures are the key to full potency. These observations challenge the value of dietary supplements containing only purified carotenoid compounds.

Broccoli confers cancer chemoprotective benefits in both epidemiological and animal studies, and 1 hydrolysis product of broccoli glucosinolates—sulforaphane—is considered its primary anticarcinogenic component. Recent investigations of food matrix influences on bioactivity showed that broccoli diets containing prehydrolyzed glucosinolates were significantly more potent than diets using comparable levels of purified sulforaphane (Keck and others 2003). Sulforaphanes delivered in the broccoli matrix may be less susceptible to binding by proteins (which would prevent absorption), thus these phytochemicals were detected in higher concentrations in the urine postfeeding. In rats fed broccoli with intact glucosinolates, quinone reductase upregulation (a biomarker for anticarcinogenesis) was significantly higher, in both liver and colon, than in animals on a control diet or on diets containing sulforaphane produced in situ by hydrolysis. Purified sulforaphane was less active than unfractionated broccoli components presented in a matrix, which suggested that other components in this vegetable (quercitin, other glucosinolate hydrolysis products, or S-methylcysteine sulfoxide) potentiated the bioactivity. Similarly, glucosinolate derivatives from another cruciferous vegetable, Brussels sprouts, were evaluated in terms of influence on phase II detoxification enzymes glutathione S-transferase, quinone reductase, and glutathione reductase. The mixture of derivatives provided more potent up-regulation of the enzymes than single components, and 2 of the breakdown products in particular (cranbene and indole-3-carbinol) demonstrated synergy responsible for the majority of the enzyme up-regulation (Staack and others 1998; Nho and Jeffery 2001).

Both the complexity and the importance of health-related phytochemical interactions are well demonstrated for the antineoplastic effects of soy components (including isoflavones). Genistein has received ample attention as a cancer-chemopreventive isoflavone in soy. When administered to prepubertal Sprague-Dawley rats orally or by injection, genistein reduced the incidence of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumors (Lamartiniere and others 1995; Murrill 1996; Fritz and others 1998). Numerous genistein dietary supplement products are now routinely available to women for use as self-prescribed natural medications. However, the apparent paradox relates to the fact that genistein is well-documented in the literature to be a plant estrogen (phytoestrogen) that binds to estrogen receptors and causes proliferation of estrogen-responsive human breast cancer cells in vitro (Martin and others 1978). Additionally, dietary genistein will stimulate proliferation of human breast cancer cells in vitro and in

vivo (Hsieh and others 1998; Allred and others 2001a, 2001b, 2004a; Cornwell and others 2004). The degree to which foods or supplements containing soy products are processed may also alter the capacity for the genistein contained in these products to stimulate estrogen-dependent tumor growth (Allred and others 2004b). Soy contains many potentially bioactive phytochemical components in addition to genistein and other isoflavones (Hosny and Rosazza 2002), thus the protective influence of multicomponent soy products is likely to be different from that of any purified component. The overall pharmacological effects of these products likely result from the complex endointeractions between their bioactive components (Cornwell and others 2004).

St. John's wort (*Hypericum perforatum* L.) is typically standardized and marketed on the basis of hypericin, pseudohypericin (antiviral components of the plant extract; Vandenbogaerde and others 1998), or hyperforin (an antidepressant component; Laakmann and others 1998). However, recently, Kirakosyan and others (2004) demonstrated that the antidepressant efficacy of hyperforin is potentiated by a synergistic interaction with the flavonoid rutin. Bisanthraquinone glycosides, which are components of St. John's wort extracts, were also elucidated in the same report as potentiating components acting with the hyperforin to elicit the antidepressant effect.

Flavonoids, which are abundant in a fruit- and vegetable-rich diet, also exhibit numerous activities that contribute to human health maintenance. Mixtures of plant flavonoids have shown additive inhibitory influence on ATPase enzymes (Zheng and Ramirez 2000) or synergistic effects on antifungal activity greater than the sum of the effects of their purified components (Silva and others 1998). A mixture of polyphenols from cranberry fruit demonstrated significantly more activity against human tumor cell lines than either a crude cranberry extract, or than individual phytochemicals from the fruits. Antiproliferative activity was clearly enhanced when anthocyanins, proanthocyanidins, and flavonol glycosides were purified by removing organic and phenolic acids and sugars, but in addition, synergistic or additive antiproliferative interactions between these semipurified co-occuring polyphenolic mixtures were indicated (Seeram and others 2004). Cranberry was recently found to have the highest soluable free phenolic content among a range of common fruits (Sun and others 2002), and the majority of antioxidant activity in the fruit was attributed to this combination of phytochemicals rather than to vitamin C content. Hou and others (2004) recently defined some of the molecular mechanisms responsible for inhibition of tumorigenesis by 6 anthocyanin pigments most common in the human diet. They showed that combinations of a superoxide dismutase (SOD) enzyme present in all plants (a scavenger of superoxide anion) and the anthocyanin delphinidin interact synergistically to inhibit the 12-*O*-tetradecanolylphorbol-13-acetate (TPA)-induced cell transformation and activator protein-1 (AP-1) transactivation, which promotes carcinogenesis. The data suggested that the inhibitory effects of anthocyanidins on AP-1 activation were due in part to their potent scavenging activity for superoxide radicals and in part to blocking mitogen-activated protein kinase (MAPK).

Ellagic acid significantly potentiated the efficacy of dietary quercetin in reducing proliferation and inducing apoptosis (Mertens-Talcott and others 2003). These polyphenolic compounds co-occur in many small fruits and in some vegetables. Negative endointeractions are exemplified by the flavonoids in freshly brewed tea, which inhibit the bioavailability of caffeine. As a result, teas have less stimulating properties than coffee, even though the former has higher overall caffeine content (Eder and Mehnert 1998).

Numerous additional examples of complex endointeractions

associated with specific plants have been documented. The potent berberine alkaloids, which are major bioactive principles in several different plant species, have coevolved with other compounds to maximize the efficacy of pleiotropic effects. The medicinal herb *Coptidis rhizoma*, for example, has demonstrated anticancer ability largely due to its berberine content. However, the crude plant extract is notably more potent than pure berberine. On the molecular level, the effects of pure berberine on anticancer genes are significantly different from the effects caused by the phytochemical mixture in the extract (Iizuka and others 2003). *Berberis fremontii* produces both antimicrobial berberine alkaloids and inhibitors of a bacterial multidrug-resistant pump that strongly potentiate the antibacterial activity of berberines (Stermitz and others 2000). Recent phase I/II double-blind, placebo-controlled trials confirmed that the strong anti-inflammatory effects produced by a root extract of a *Tripterygium wilfordii* are due to blocking the expression of a number of pro-inflammatory genes including cyclooxigenase-2, inducible nitric oxide synthase, and several inflammatory interleukins (Tao and others 2002). The primary bioactive component in this traditional Chinese medicinal plant has been identified as diterpenoid triptolide. However, it is too toxic and less effective unless given as a part of the root extract, suggesting that other unidentified extract components increase its safety and, possibly, efficacy (Su and others 1990). The overall mild diuretic effects of plants such as *Solidago virgaurea* (goldenrod), *Betula* (birch), and *Ononis spinosa* (rest harrow) result from the combination of natural flavonoids, saponins, and volatile oils they contain, and no single component can match the potency of the mixture (Pietta 1998). Potentiating phytochemical interactions between the terpene lactones (ginkgolides and bilobalide) that are platelet-activating factors and the flavonoid antioxidants (mostly proanthocyanidins and rutins) and microcirculation enhancers may account for wide range of effects of ge:*Ginkgo biloba* extract (De Feudis 2003).

Similarly, synergy has been demonstrated between vitamin C and vitamin K_3 in the diet, which together inhibit tumorigenesis (von Gruenigen and others 2003). Also, whole grain consumption, as opposed to consumption of refined grain, lowers risks of some chronic disease (including ischemic stroke and coronary artery disease), indicating that all edible parts of the plant materials (bran germ and endosperm) are required for full potency (Jacobs and Steffen 2003). Several of the edible spices have shown various, simultaneous bioactivities including anticancer capacity, pesticidal properties, anti-inflammatory, antioxidant capacity, and antispasmolytic activity (Beckstrom-Sternberg and others 1994). In all of these diverse cases, endointeractions modulate the pharmacological properties associated with the plant or plant products.

Exointeractions

The notions that foods, drugs, and dietary supplements of plant origin may interact with each other and with conventional pharmaceuticals is well accepted, but until recently, relatively poorly documented. When discussing exointeractions, foods and dietary supplements can be treated as 1 category because both usually represent complex mixtures of ingested compounds. Also, new foods and dietary supplements are regulated differently than drugs, and many do not undergo extensive toxicity testing and rigorous human trials before being sold to the public.

The majority of food-drug interactions characterized so far are caused by the effects of phytochemicals on the bioavailability of the drug. Phytochemicals that alter bioavailability by interfering with drug metabolizing systems, such as cytochrome P450s, have probably generated the broadest attention and were the subject of 2 excellent recent reviews (Harris and others 2003; Ioannides 2003).

Table 2—Best documented exointeractions between dietary supplements, foods, and drugs*

Negative interactions	
Phytochemical source	Reduces of activity for the drug below
Cruciferous vegetables	Phenacetin, caffeine
St. John's wort	Cyclosporin, indinavir, warfarin, theophylline, digoxin, psychotropic and narcotic agents, contraceptives
Garlic	Saquinavir
High fiber	Digoxin and lovastatin
Phylloquinone from green vegetables	Warfarin
Echinacea	Corticosteroids
Positive interactions	
Phytochemical source	Enhances activity for the drug below
Citrus juice	Felodipin, cyclosporine, erythromycin, ethinyloestradiol, lovastatin, midazolam, saqunavir, terfenadine, triazolam, quinidine
Vegetable oils	Albendazole, isotretinoin, griseofulvin, halofantrine
Gingko biloba, kava kava, echinacea	Barbiturates
Ginkgo biloba, ginseng	Aspirin
Piperine from pepper	Phenytoin, theophylline, propranolol
Garlic	Antihypertensive and antidiabetic drugs, aspirin, clopidogrel, warfarin
Hawthorne	Antihypertensive drugs

[a]All examples are referenced in the text.

Table 3—Mechanisms of common exointeractions[a]

Mechanism	Source
Cytochrome P450 inhibition	Isothiocyanates from cruciferous vegetables
	Furanocoumarins from grapefruit juice
Cytochrome P450 activation	Hyperforin from St. John's wort
P-glycoprotein activation	St. John's wort
P-glycoprotein inhibition	Furanocoumarins from grapefruit juice
Glutathione S-transferases and glucuronyl transferases activation	Indoles from cruciferous vegetables
Enhanced drug solubility and uptake	Vegetable oils

[a]All examples are referenced in the text.

Because phytochemicals may both suppress and stimulate P450 enzymes, it is not surprising that they may interfere with the effect of a variety of drugs. Phytochemicals that stimulate P450 systems will reduce the effectiveness of drugs, whereas phytochemicals that inhibit P450 systems will generally prolong and strengthen the effect of the drug, creating an overdose-like effect. Most food-drug interactions summarized in Table 2 and 3 could be placed in the categories discussed subsequently.

Negative interferences based on enhanced drug metabolism and reduced uptake

An early demonstration of the negative interference between food and drugs came from the observation that diet supplemented with cruciferous vegetables lowered plasma levels of analgesic phenacetin in people (Pantuck and others 1979). This effect was

attributed to the stimulation of CYP1A activity by indole compounds that are present in high concentrations in broccoli and Brussels sprouts used in the experiments. Similarly, 3 meals of cruciferous vegetables were sufficient to reduce the half-life of caffeine in people by about 20% (McDanell and others 1992). Animal studies have demonstrated that the stimulatory effect of dietary indoles on the CYP1A family likely occurs at the transcriptional level (Vang and others 1990). Indoles from cruciferous vegetables were also shown to stimulate conjugation reactions carried out by glutathione S-transferases and glucuronyl transferases that may further enhance drug metabolism via non-P450 mechanisms (Pantuck and others 1984). Although less important for drug metabolism than cytochrome P450 enzymes, glutathione S-transferases and glucuronyl transferases are involved in many xenobiotic detoxification processes in animals and alterations in their activity may change efficacy and safety profiles of drugs.

Unfortunately, the story of cruciferous vegetables and xenobiotic metabolism is made more complex by the presence of isothiocyanates, other nitrogenous phytochemicals that are released from their precursors, glucosinolates, after the disruption of the cells of cruciferous vegetables by cooking, processing, or chewing. At least in vitro, isothiocyanates can down-regulate human cytochrome P450s (Nakajima and others 2001) while up-regulating glutathione S-transferases (Mahéo and others 1997). Phenethyl isothiocyanate, produced in abundance by wintercress (Ribnicky and others 2001), may reduce cancer risk in smokers by blocking the cytochrome P450–mediated metabolic activation of the common nitrosamine, NNK [nitrosoamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone], to its potent carcinogenic forms (Conaway and others 1996; Ribnicky and others 2001). Many other phytochemicals from noncruciferous vegetables were also shown to influence cytochrome P450 system in vitro (Ioannides 2003). However, their effect in vivo, particularly in people, is not as well documented.

Because the 1st description of the interactions of pharmacologically active compounds with phytochemicals in cruciferous vegetables in 1979 (Pantuck and others 1979), it became clear that the general public and physicians are only seeing the tip of the iceberg of potentially dangerous phytochemical exointeractions. Following the passage of the Dietary Supplement and Health Education Act of 1994 (DSHEA), botanical nutraceuticals (dietary supplements) became a permanent fixture on the shelves of supermarkets, drug stores, and health food stores. Wide use of these poorly tested or chemically defined botanical products expose the human population to an array of phytochemicals that is not present in the regular diet. And it did not take long for physicians to observe that some of the commonly used dietary supplements affect the efficacy and safety of drugs.

St. John's wort (*Hypericum perforatum*) extract, considered a remedy for mild depressions and various cardiovascular ailments, probably represents the best-studied example of drug/nutraceutical interaction to date. An increasing number of interactions of St. John's wort with drugs have been recently described in the literature. Of these, the negative interaction with the immunosuppressant drug cyclosporin commonly used to prevent rejection in transplant patients is most dangerous and best studied. Several studies have shown that St. John's wort simultaneously stimulates an increase in intestinal CYP3A4 activity and an increase in the expression of the P-glycoprotein in the intestine (for review, see Ioannidis 2003). The 1st protein is believed to be responsible for the metabolism of cyclosporin and other large-molecular-weight drugs, whereas the 2nd acts as a membrane-localized drug-transport mechanism that has the ability to actively pump out xenobiotic compounds from cells, limiting their bioavailability. These findings

were confirmed by both in vitro experiments (Carson and others 2000; Dürr and others 2000) and in humans (Dürr and others 2000; Roby and other 2000). Hyperforin is a major component of St. Johns wort and 1 of the compounds believed to be responsible for the antidepressant effect of this herb. Hyperforin also stimulates CYP3A4 activity (Budzinski and others 2000), which is at least partially responsible for the enhanced metabolism of cyclosporin.

Following observations of the negative interactions between St. John's wort and cyclosporin, St. John's wort–derived nutraceuticals were shown to cause negative interactions with anti-HIV protease inhibitor indinavir, anticoagulant warfarin, anti-asthmatic theophylline, cardiac glycoside digoxin, and psychotropic and narcotic agents (Harris and others 2003; Ioannides 2003). In addition, women taking St. John's wort together with a contraceptive pill experienced bleeding attributed to an increased deactivation of the steroids through CYP3A-mediated metabolism (Ernst 1999). All of these negative interactions could be functionally attributed to the St. John's wort–induced reduction of drug concentration in blood. Another recent human trial evaluated the effects of long-term supplementation with St John's wort, garlic oil, *Panax ginseng* (ginseng), and *Ginkgo biloba* on CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity reflected in the metabolism of marker drugs administered before and after supplementation (Gurley and others 2002). St John's wort significantly induced the activity of CYP2E1 and CYP3A4, particularly in female volunteers. Garlic oil reduced CYP2E1 activity, whereas no significant effect on cytochrome P450 activity was observed for ginseng and *Ginkgo biloba*. As a somewhat contradictory result, human studies have also shown that garlic may induce intestinal cytochrome P450s (CYP3A4) and cause clinically important negative interactions with a variety of drugs, such as saquinavir, an HIV protease inhibitor. Consumption of garlic by healthy volunteers resulted in approximately 50% decrease in exposure to saquinavir (Piscitelli and others 2002).

Potentiation based on reduced metabolism and enhanced uptake

While induction of cytochrome P450 enzymes by phytochemicals generally leads to negative interferences with drugs, inhibition of cytochrome P450 may lead to significant and usually undesirable potentiation of drug effects. This potentiation clinically manifests itself as a drug overdose. Enhancement of the effects of several drugs by grapefruit juice is probably the best-studied example of potentiation achieved through the inhibition of cytochrome P450s. Early studies demonstrated that grapefruit juice, when taken together with hypertension-reducing calcium channel blocker (felodipin), led to higher blood levels of the drug, concomitantly greater reduction in blood pressure, and exaggerated side effects compared with felodipin taken with water (Bailey and others 1991). In the next decade, the potentiating effects of grapefruit juice on many other drugs (cyclosporine, erythromycin, ethinyloestradiol, lovastatin, midazolam, saqunavir, terfenadine, triazolam, and quinidine) were documented (for review, see Ioannides 2003). It is widely believed that the strong inhibitor effects of furanocoumarins from grapefruit juice on the intestinal cytochrome P450 enzymes involved in drug metabolism cause these effects (Lown and others 1997; Edwards and others 1999). In addition, phytochemicals present in grapefruit juice may facilitate drug absorption by inhibiting P-glycoprotein cellular efflux pumps (Soldner and others 1999) and/or organic anion transporting polypeptide (OATP) that directly facilitates drug uptake (Dresser and others 2002). The potentiating effects of grapefruit juice on drug efficacy, which may last for several days (Takanaga and others 2000), should be a particular concern to patients and physicians. Because grape-

fruit juice contains a diverse collection of monomeric and dimeric furanocoumarins, the relative contribution of these compounds to the overall drug potentiating effect of grapefruit juice is a subject of continuous discussion (Ioannides 2003). However, dimers of furanocoumarins are more potent inhibitors of intestinal P450s than monomers. Some studies have shown that some brands of orange juice may be as effective as grapefruit juice in producing overdose-like effects of many medications (Malhotra and others 2001). Interestingly, while furanocoumarins found in citrus fruits potentiate the effects of drugs, citrus pectins fed to rats significantly depressed the bioavailability of beta-carotene, a precursor of vitamin A (Zanutto and others 2002).

Other plant food-drug interactions

Interactions based on the physiochemical properties of major plant food components probably represent the largest part of other described food-drug interactions (for review see Schmidt and Dalhoff 2002). For example, fatty foods that include vegetable oils may increase the bioavailability of lipophilic drugs simply by increasing drug solubility as shown for albendazole and isotretinoin. High-fat food may also stimulate drug absorption by stimulating bile secretion as shown for griseofulvin and halofantrine. Alternatively, high-fiber cereals may reduce the bioavailability of certain drugs, such as digoxin and lovastatin, because of their binding to cellulose and other charged plant polysaccharides. Evidence also suggests that the major tomatocarotenoid, lycopene, possessing strong antioxidant activity, and marketed as a beneficial dietary supplement, is much more bioavailable when ingested with oils as a component of tomato paste or pizza (Gartner and others 1997; Williams and others 1998). Certainly more research in this area will uncover more potential drug-food interactions based on nonmetabolic mechanisms.

Recently, particular attention was given to possible interactions between anesthetics and botanical dietary supplements. While the mechanism of many of these interactions remains unknown, it is clear that dangerous or life-threatening situations may result from the use of some dietary supplements before surgery. Numerous studies have shown that botanical supplements such as garlic, ginger, gingko, and ginseng increase bleeding time, which can cause an increased risk during surgery (Rose and others 1990; Rowin and Lewis 1996; Kaye and others 2000). In addition, *Gingko*, kava kava, and echinacea were reported to interact with barbiturates that are used freely in the practice of anesthesiology and can cause increased sedation while ephedra may interact with volatile anesthetics such as halothane, desflurane, or isoflurane (Sabar and Kaye 2000; Kaye and others 2000). A recent clinical survey has documented that 32% of patients admitted to self-administering 1 or more botanical supplements (Kaye and others 2000). Nearly 70% of patients who were taking 1 or more botanical supplements did not report this information when asked during routine anesthetic assessment.

A number of other exointeractions were documented in the literature without a clear understanding of the mechanisms of the observed interactions. For example, piperine, an alkaloid from white and black pepper that may alter membrane fluidity (Khajuria and others 2002), potentiated the effects of the antiepileptic drug phenytoin (Bano and others 1987), theophylline, and the beta-blocker propranolol (Bano and others 1991) in humans. Phylloquinone (natural vitamin K involved in blood clotting) is present at high levels in dark leafy greens such as Swiss chard, spinach, and broccoli. Consumption of much these vegetables in the diet negatively interfered with the blood-thinning effect of warfarin reducing its clinical effectiveness (Karlson and others 1986). Resveratrol,

a dietary polyphenolic with anticancer properties, may potentiate the effects of other chemotherapeutic drugs in drug-resistant tumor cells (Cal and others 2003). A recent survey of elderly people suggested that garlic, the most commonly used botanical dietary supplement, potentiated the effects of antihypertensive drugs, antidiabetic drugs, aspirin, clopidogrel, and warfarin; flaxseed and psyllium decreased absorption of all drugs used by patients; *Ginkgo biloba* and ginseng potentiated the blood-thinning effect of aspirin; Hawthorne potentiated the effects of antihypertensive drugs; and echinacea blunted the immunosuppressive effect of corticosteroids (Ly and others 2002). Some food components, such as large-molecular-weight tannins and related polyphenols, contain multiple charged groups and, thus, may cause direct precipitation and/or binding inactivation of drugs or bioactive agents (Kraus and others 2003). Tannins may also interfere with the enzymes in the digestive system altering the bioavailability of pharmaceutical agents. Although most of these effects are not yet well substantiated, they should be an important area for future studies.

Interactions between foods in regional diets represent an even more complex and less understood form of phytochemical interplay. Multiple health- and wellness-promoting properties of edible plants have been cited as instrumental factors in a healthy life style. Diet components may act synergistically to influence the risk of several chronic diseases. The Mediterranean diet, rich in flavonoids from nuts, beneficial fatty acids, and phenolic compounds from olive oil, stilbenes, proanthocyanins, and other flavonoid compounds from grapes and berries, provitamins, antioxidants, and carotenoids, is purported to be particularly effective due to the interactions between these pharmacologically active phytochemicals (Gerber 2003). Ischemic heart disease is a multifactorial syndrome with a complex etiology. Lower incidence of this disease in the Mediterranean region has been linked to the characteristic diet, and, in particular, to the interactions between the above compounds that allegedly act together to promote cardiovascular health (Rajaram 2003). Similarly, the combined effects of soy and tea bioactive agents prevalent in Asian diets proved to synergistically inhibit human breast tumor growth (Zhou and others 2004) and inhibit human prostate cancer cell growth in a dose-dependent manner (Sakamoto 2000). A significant synergistic increase in growth arrest in response to DNA damage in genes is realized when a dimer of indole-3-carbinol (from cruciferous vegetables) is delivered along with the soy isoflavone genistein (Auborn and others 2003).

The relative infancy of our knowledge of botanical food supplement–drug interactions and the complexity of scientific issues involved is probably best demonstrated by the interaction of phytoestrogens and breast cancer drugs. One in 8 woman living in the United States will develop breast cancer over her lifetime. Because the risk of this disease is often associated with estrogen balance, foods and supplements containing phytoestrogens, such as soy extracts, have been historically recommended to decrease the incidence and reoccurrence of the disease. This recommendation was primarily based on relatively poor epidemiological evidence. However, recently documented cell-proliferating effects of many phytoestrogens have seriously questioned this use, and numerous clinical studies have not clearly proved the benefits of phytoestrogens in cancer treatment and prevention (for review, see Cornwell and others 2004). Because of the importance of breast cancer and the enormous impact of this disease on women's health, it is important to define the nature of interactions of phytoestrogens with oral drugs used to treat breast cancer. These drugs include estrogen action inhibitor, tamoxefen, and the inhibitors of estrogen synthesis, aromatase inhibitors. Both classes are routinely used after

breast cancer surgery and in high-risk patients and are taken for many years. At present, doctors do not generally recommend the use of phytoestrogen-containing soy supplements in combination with these drugs. However, greater understanding of the interactions between these phytochemicals and drugs is required to provide recommendations that could save patients' lives.

Conclusions

Successful treatment and prevention of complex chronic diseases almost always requires multicomponent therapy to deal with their multiple symptoms and causes. Because current regulations make the development of even simple multicomponent pharmaceuticals impractical and expensive, the common clinical solution is to provide patients with a cocktail of drugs, most with a single active ingredient. The realities of the intensely competitive and regulated pharmaceutical industry dictate that more efforts are placed on the study of negative drug-drug interactions than on the evaluation of potential beneficial synergy between various components of drugs and foods. Also negative interactions are much easier to observe, quantify, and study. That is why most of the exointeraction section of this review is dedicated to the undesirable effects of combining botanical foods, supplements, and drugs. Unfortunately, clinically desirable interactions are much harder to define, and yet they may represent the new frontier of medicine where the pharmacological effects of many components of foods, drugs, and supplements are working together to better fight or prevent diseases.

The study and development of these multicomponent therapies may require approaches and technologies not yet developed. However, the USFDA-proposed category of botanical drugs (http://www.fda.gov/cder/guidance/1221dft.htm), which regulates the development of standardized botanical mixtures and a more recent allowance of qualified health claims on foods and supplements (http://www.cfsan.fda.gov/~dms/hclmgui3.html), may stimulate more research into multicomponent botanicals.

Acknowledgments

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