Chapter 14
Risks Involved in the Use of Herbal Products

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Abstract The use of different herbal products can involve several kinds of risks that include improper labeling or failure to provide the correct constituents; inadequate testing of the herbal product in clinical trials; failure to provide the stated amounts of active constituents; contraindications between known herbs and synthetic prescription drugs used to treat the same disease; overdosing or underdosing; contamination of herbal preparations with pathogens, pesticides, and heavy metals; expired shelf life; and problems with formulations that render them ineffective (e.g., ineffective dried preps in capsules versus effective formulations taken as tinctures). In this chapter, we shall address many of these issues. They are basically issues of quality control that involve the latest advances in plant biotechnology.

14.1 Compromised Quality in the Preparation of Herbal Medicines

Herbs to be grown for the preparation of herbal medicines can be compromised in their quality for the following reasons:

- Herbs obtained from different sources (countries, regions, and growers) are mixed in order to make commercial preparations.
- Herbs are not grown under uniform field or greenhouse conditions from year to year.
- Herbs are not collected at the optimum stage of development.
- Herbs collected are adulterated with other herbs, some of which may be toxic or devoid of the same biological activity.

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- Processing of herbs after collection (e.g., drying or freeze-drying) is not uniform. Herbs are often sun-dried in the field and, as a result, lose much of their potency.
- Processed herbs are not packaged or stored properly before commercial sale.
- Herbs are adulterated with other constituents (e.g., preservatives and fillers) when packaged for commercial sale.

In order to mitigate these problems, growers and processors need to use standard conditions and guidelines for growing, harvesting, formulating, and packaging of herbal preparations. Good sources for this kind of information are found in Ody (1993) and Moore (1995).

14.2 Inadequate Testing of Herbal Medicine Products

Many medicinal herbs have not yet been subjected to testing in human clinical trials. Instead, they are promulgated for use based on animal (nonhuman) models or based on oral tradition or practices of shamans.

Even if human clinical trials are conducted, they can suffer from improper design. For example, this can include the following:

- Failure to use a double-blind, placebo-controlled, randomized clinical trial protocol.
- Failure to include greater than a single biologically active dose. The best judgment here is to include half optimum, optimum, and twice optimum levels/doses of the herb.
- Failure to include a sufficient number of time points to do good kinetics or to obtain meaningful data.
- Failure to carry out the study for a sufficient length of time. This is especially critical for many herbal preparations, which often tend to be slow acting or require administration of prescribed doses over an extended period of time (not hours or days, but weeks).

14.3 Risks in the Use of Medicinal Herbs

The use of medicinal herbs to treat specific human disease can involve risks, especially when used in combination with different kinds of synthetically produced prescription drugs. Patients taking herbal medicines as well as prescription drugs to treat a specific ailment must consult their doctor before using such combinations.

Examples (cited in The Merck Manual of Medical Information, second home edition, 2004, by Mark H. Beers) of such adverse interactions are given in Table 14.1.

Table 14.1 Some possible medicinal herb–drug interactions

Medicinal herb	Affected drugs	Interaction
Chamomile	Anticoagulants (such as warfarin)	Chamomile taken with anticoagulants may increase the risk of bleeding
	Barbiturates (such as phenobarbital) and other sedatives	Chamomile may intensify or prolong the effects of sedatives
	Iron	Chamomile may reduce iron absorption
Echinacea	Drugs that can damage the liver (such as anabolic steroids, amiodarone, methotrexate, and ketoconazole)	Echinacea taken for more than 8 weeks may damage the liver. When echinacea is taken with another drug that can damage the liver, the risk of liver damage may be increased
	Immunosuppressants (such as corticosteroids and cyclosporine)	By stimulating the immune system, echinacea may negate the effects of immunosuppressants
Feverfew	Anticoagulants (such as warfarin)	Feverfew taken with anticoagulants may increase the risk of bleeding
	Iron	Feverfew may reduce iron absorption
	Drugs used to manage migraine headaches (such as ergotamine)	Feverfew may increase heart rate and blood pressure when it is taken with drugs used to manage migraine headaches
	Nonsteroidal anti-inflammatory drugs (NSAIDs)	NSAIDs reduce the effectiveness of feverfew in preventing and managing migraine headaches
Garlic	Anticoagulants (such as warfarin)	Garlic taken with anticoagulants may increase the risk of bleeding
	Drugs that decrease blood sugar levels (hypoglycemic drugs such as insulin and glipizide)	Garlic may intensify the effects of these drugs, causing an excessive decrease in blood sugar levels (hypoglycemia)
	Saquinavir (used to treat HIV infection)	Garlic decreases blood levels of saquinavir, making it less effective
Ginger	Anticoagulants (such as warfarin)	Ginger taken with anticoagulants may increase the risk of bleeding
Ginkgo	Anticoagulants (such as warfarin), aspirin, and other NSAIDs	Ginkgo taken with anticoagulants or with aspirin or other NSAIDs may increase the risk of bleeding
	Anticonvulsants (such as phenytoin)	Ginkgo may reduce the effectiveness of anticonvulsants in preventing seizures

Table 14.1 (continued)

Medicinal herb	Affected drugs	Interaction
	Monoamine oxidase inhibitors (MAOIs, a type of antidepressant)	Ginkgo may intensify the effects of these drugs and increase the risk of side effects, such as headache, tremors, and manic episodes
Ginseng	Anticoagulants (such as warfarin), aspirin, and other NSAIDs	Ginseng taken with anticoagulants or with aspirin or other NSAIDs may increase the risk of bleeding
	Drugs that decrease blood sugar levels (hypoglycemic drugs)	Ginseng may intensify the effects of these drugs, causing an excessive decrease in blood sugar levels (hypoglycemia)
	Corticosteroids	Ginseng may intensify the side effects of corticosteroids
	Digoxin	Ginseng may increase digoxin levels
	Estrogen replacement therapy	Ginseng may intensify the side effects of estrogen
	MAOIs	Ginseng can cause headache, tremors, and manic episodes when it is taken with MAOIs
	Opioids (narcotics)	Ginseng may reduce the effectiveness of opioids
Goldenseal	Anticoagulants (such as warfarin)	Goldenseal may oppose the effects of anticoagulants and may increase the risk of blood clots
Licorice	Antihypertensives	Licorice may increase salt and water retention and increase blood pressure, making antihypertensives less effective
	Antiarrhythmics	Licorice may increase the risk of an abnormal heart rhythm, making antiarrhythmic therapy less effective
	Digoxin	Because licorice increases urine formation, it can result in low levels of potassium, which is excreted in urine. When licorice is taken with digoxin, the low potassium levels increase the risk of digoxin toxicity
	Diuretics	Licorice may intensify the effects of most diuretics, causing increased, rapid loss of potassium. Licorice may interfere with the effectiveness of potassium-sparing diuretics, such as spironolactone, making these diuretics less effective
	MAOIs	Licorice may intensify the effects of these drugs and increase the risk of side effects, such as headache, tremors, and manic episodes

Table 14.1 (continued)

Medicinal herb	Affected drugs	Interaction
Milk thistle	Drugs that decrease blood sugar levels (hypoglycemic drugs)	Milk thistle may intensify the effects of these drugs, causing an excessive decrease in blood sugar levels
	Saquinavir	Milk thistle decreases blood levels of saquinavir, making it less effective
Saw palmetto	Estrogen replacement therapy and oral contraceptives	Saw palmetto may intensify the effects of these drugs
St. John's wort	Benzodiazepines	St. John's wort may reduce the effectiveness of these drugs in reducing anxiety and may increase drowsiness and the risk of side effects such as drowsiness
	Cyclosporine	St. John's wort may reduce blood levels of cyclosporine, making it less effective, with potentially dangerous results (such as rejection of an organ transplant)
	Digoxin	St. John's wort may reduce blood levels of digoxin, making it less effective, with potentially dangerous results
	Indinavir (a drug used to treat AIDS)	St. John's wort may reduce blood levels of indinavir, making it less effective
	Iron	St. John's wort may reduce iron absorption
	MAOIs	St. John's wort may intensify the effects of MAOIs, possibly causing very high blood pressure that requires emergency treatment
	Photosensitizing drugs (such as lansoprazole, omeprazole, piroxicam, and sulfonamide antibiotics)	When taken with these drugs, St. John's wort may increase the risk of sun sensitivity
	Selective serotonin reuptake inhibitors (such as fluoxetine, paroxetine, and sertraline)	St. John's wort may intensify the effects of these drugs
	Warfarin	St. John's wort may reduce blood levels of warfarin, making it less effective and clot formation more likely
Valerian	Anesthetics	Valerian may prolong sedation time
	Barbiturates	Valerian may intensify the effects of barbiturates, causing excessive sedation

*14.3.1 Medical Risks in the Use of Kava Kava (***Piper methysticum***): A Case Study*

Kava kava is a herbal ingredient derived from the plant *Piper methysticum* G. Forst., which is a member of the pepper family (Piperaceae). It is native to many Pacific Ocean islands. The leaves and the root of the plant are used in herbal food and medicinal products. In recent years it has become popular in Europe in herbal remedies used to treat anxiety, tension, and restlessness.

It is considered a sacred plant by many of the traditional Polynesian cultures and has been used in prayer and ritual as well as for a wide variety of ailments ranging from asthma and rheumatism to weary muscles and sleeplessness. The main active components in kava kava (kavalactones) are found in the root of the plant. Kavalactones are thought to affect levels of neurotransmitters in the blood, which can affect the body's fight-or-flight response. While kava root was traditionally chewed or made into a beverage, it is now primarily taken as a natural anxiety remedy in capsule, tablet, beverage, tea, and liquid extract forms.

Evidence has mounted that in rare cases the use of products containing kava kava (mostly in the form of herbal medicines) has been associated with severe liver damage. Research indicates that this may be largely due to the use of stems and leaves in dietary supplements, which were not used indigenously. The occurrence of liver damage is unpredictable and the mechanism is unclear. Some of the compounds found in Kava extracts block several subtypes of the enzyme cytochrome P450, which may result in adverse interactions with concomitant use of other drugs and alcohol (Mathews et al., 2002). Because of these reports, regulatory agencies in Europe and Canada now warn consumers of the potential risks associated with kava kava and even remove kava-containing products from the market. Based on these and other reports in the United States, the Food and Drug Administration (FDA) issued a consumer advisory in March of 2002 regarding the "rare" but potential risk of liver failure associated with kava-containing products.

*14.3.2 Medical Risks in the Use of Ephedra (***Ephedra sinica***): A Case Study (Modified from Data Provided by www.rand.org/health)*

The herb **ephedra**, also known as **ma huang** (*Ephedra sinica* Stapf.), is a small shrub native to Asia, where it has a long history of medicinal use, as documented in ancient medical treatises from India and China. In traditional Chinese and Indian medicine, branches of the herb are used to treat colds, and it is also used as a diuretic. Modern European practitioners of herbal medicine use ephedra only to treat symptoms of respiratory diseases, such as bronchial asthma.

In the United States, the active components of ephedra are known as **ephedrine alkaloids.** They include ephedrine, pseudoephedrine, and norephedrine (also known as phenylpropanolamine and norpseudoephedrine). These constituents are

commonly found in over-the-counter cold and allergy medications. The ephedrine alkaloids are stimulants similar to, but much weaker than, amphetamines. These ephedra stimulants can increase heart rate and blood pressure and relax bronchial tissue, easing shortness of breath. At low doses, they are reputed to decrease appetite, increase alertness and productivity, improve mood, and decrease fatigue; at higher doses, they may promote anxiety, restlessness, and insomnia.

The use of ephedra to promote weight loss and to enhance athletic performance began to gain popularity in the United States in the early 1990s. The increase in popularity of herbal products, and over-the-counter medications that seem to promote weight loss, is probably due to a combination of factors. These include the recent precipitous rise in obesity rates, the reluctance of many obese people to talk with their doctors about weight control, and the growing belief on the part of many people that natural substances such as herbs are safer to use than synthetic prescription medicines.

Products that contain the herb ephedra have been promoted and used in the United States since the 1980s in order to increase weight loss and to enhance athletic performance. Yet, despite manufacturers' claims, little research has been done to assess whether or not ephedra products are safe. Furthermore, the research studies that have been done have been too small to allow any firm conclusions to be drawn.

The questionable effectiveness of these products might not have raised public concern, had the **US Food and Drug Administration (FDA)** and major manufacturers of ephedra-containing products not become the targets of growing numbers of consumer complaints in the late 1990s. Reports of adverse events, including serious adverse side effects and even deaths, many in apparently healthy young people, began increasing during this time. Prominent among the victims have been several college and professional athletes. Thus, in recent years, several major consumer health groups have called on the FDA to ban sales of ephedra-containing products.

The FDA classifies products containing herbal ephedra as dietary supplements, which are regulated by the Dietary Supplement Health and Education Act of 1994 (DSHEA). Under the DSHEA, dietary supplements are generally "presumed safe." Thus, manufacturers are required only to notify the FDA of their intent to market new products. However, they are not required to establish the safety or the effectiveness of their products. Once a dietary supplement is on the market, the FDA can restrict its use or ban sales of the product only if it can demonstrate convincingly that the product is unsafe.

The studies that have been conducted (see Shekelle et al., 2003a and 2003b) suggest that ephedra- and ephedrine-containing products may be modestly effective in promoting weight loss, but the evidence on enhancing athletic performance is not definitive. However, the use of ephedra or ephedrine does cause an increase in jitteriness, mood changes, palpitations, nausea, and vomiting. Moreover, the adverse-event reports raise serious concerns about the safety of ephedra and ephedrine products.

In response to the reporting of these studies, the federal government quickly moved to propose stricter labeling of ephedra products and solicited public comment

on whether the safety evidence thus far warrants further restrictions. By itself, the existing evidence is insufficient to link these products conclusively with death and other serious health problems. However, an analysis of the existing studies and their shortcomings suggests that a more definitive answer to questions about ephedra's safety could be obtained by doing what is called a **"case–control" study**.

Such a study would compare ephedra use by individuals who suffered death or another illness with use by similar individuals who have not suffered severe health problems. A study of this type could also be used to compare the safety of ephedra-containing supplements and products containing ephedrine. Finally, a case-control study could help answer safety questions quickly, thus avoiding the expense and time that would be needed to conduct a large-scale randomized controlled trial and potentially saving lives.

14.3.3 Risks Associated with the Use of Vaccinium*: A Case Study*

The genus *Vaccinium* is composed of approximately 450 species, many of which have been important food and medicinal plants for cultures worldwide throughout the millennia. All are considered nontoxic, although palatability and composition across such a wide range of species are, understandably, diverse. Interest in *Vaccinium*-based dietary supplements has increased dramatically over the past decade as consumers have become aware through the media of the numerous health benefits of *V. corymbosum* (highbush blueberry) and *V. angustifolium* (lowbush or "wild" blueberry). In fact, these fruits have been categorized, among a select group of other fruits and vegetables, as "superfoods" in consumer-oriented marketing campaigns. Although this claim is arguably legitimate, based on their replete flavonoid content and generally recognized safety profile, some considerations must apply.

Consumers face a dizzying array of products based on *Vaccinium* in the form of capsules, powders, liquid formulas, sports drinks, energy bars and as an ingredient in dairy, grain, and other food matrices. Although consumers are familiar, conceptually, with antioxidants and free radicals, they are often misled by claims of superior antioxidant activity of different products, which are usually based only on testing of a limited spectrum of antioxidant activities. One group sought to compare directly and make example of various commercial fruit juices through (1) evaluation of the total polyphenol content [by gallic acid equivalents (GAEs)]; (2) four tests of antioxidant potency including Trolox equivalent antioxidant capacity (TEAC), total oxygen radical absorbance capacity (ORAC), free radical scavenging capacity by 2,2-diphenyl-1-picrylhydrazyl (DPPH), and ferric reducing antioxidant power (FRAP); and (3) a test of antioxidant functionality, that is, inhibition of low-density lipoprotein (LDL) oxidation by peroxides and malondialdehyde methods of polyphenol-rich beverages in the marketplace (Seeram et al., 2008). In this study, total polyphenol content, composite antioxidant potency, and ability to inhibit LDL oxidation were consistent in classifying the antioxidant capacity of the polyphenol-rich beverages in descending order: *Punica granatum* L. (pomegranate)

juice > red wine > *Vitis x labruscana* (Concord grape) juice > *V. corymbosum* (blueberry) juice > *Prunus serotina* Ehrh. (black cherry) juice, *Euterpe oleracea* Mart. (a,caí) juice, *V. macrocarpon* (cranberry) juice > *Citrus sinensis* (L.) Osbeck (orange) juice, iced tea beverages, *Malus domestica* Borkh. (apple) juice.

While these results are interesting and arguably legitimate, different sample brands could alter readily the order of observed antioxidant potency. In many products, the amount of *Vaccinium* included is often very low, although its contribution to the final product may be inflated through labeling in order to use it as the marketing "handle." Furthermore, the quality of *Vaccinium* preparations used in a finished product, whether in dried or extract forms, may be inconsistent. The fresh fruit source is of utmost importance, as notable differences have been documented not only between species but also between cultivars, growth conditions, harvest time, storage, and ultimate processing – even for the same species. Drying technologies differ in terms of temperature and time required for the process, and the amount of flavonoids retained, especially the anthocyanins, significantly decreases under harsher conditions. Similarly, the yield of bioactive flavonoids is dependent upon the method employed to produce an extract. In recent years, advanced analytical methods have become available to assess the authenticity and quality of *Vaccinium* compositions for research purposes and standardization of commercial products for dietary supplements and clinical applications (Zhang et al., 2004; Määttä-Riihinen et al., 2004; Tian et al., 2005; Burdulis et al., 2007; Cassinese et al., 2007; Harris et al., 2007; Lin and Harnly, 2007; Grant and Helleur, 2008). Whereas the quality control of herbal medicinal products used by health-care practitioners is regulated in detail (e.g., German Commission E), no uniform requirements for food-derived supplements currently exist. A **standardized preparation**, typically an extract, is one with a consistent and guaranteed percentage of a definable bioactive compound or group of compounds. For *Vaccinium* dietary supplements, standardization is a voluntary effort by manufacturers to offer a high-quality product. The principal components of interest from *Vaccinium*, anthocyanins and proanthocyanidins, are notoriously difficult among all flavonoids to analyze quantitatively with accuracy (Krenn et al., 2007). Yet other biotechnological methods have been developed to improve yield and composition and mitigate against detrimental effects of storage and processing on the stability of flavonoids from *Vaccinium* in foods, nutraceuticals, and phytopharmaceutical dosage forms (Kalt et al., 1999; Connor et al., 2002; Gunes et al., 2002; Wang and Stretch, 2002; Lyons et al., 2003; Zheng et al., 2003; Lohachoompol et al., 2004; Vattem et al., 2005; Song and Sink, 2006; Srivastava et al., 2007; Puupponen-Pimiä et al., 2008; Brambilla et al., 2008; Wang et al., 2008).

Since flavonoids are known to be potent antioxidants, and compartments such as plasma, tissues, and urine have been shown to increase in antioxidant capacity following consumption of flavonoid-rich substances, a reasonable assumption is that they are readily bioavailable (Cao and Prior, 1998; Prior and Cao, 1999; Prior and Cao, 2000; Vinson et al., 2008). In fact, flavonoids are relatively abundant micronutrients in the diet, but bioavailability differs greatly from one type to another. Thus,

the most abundant dietary flavonoids are not necessarily those leading to the highest concentrations of active metabolites in target compartments.

Employing data from 97 studies, based on a single ingestion of pure compound, extract, or whole food/beverage, one group of investigators calculated mean values for the maximal plasma concentration, the time to reach the maximal plasma concentration, the area under the plasma concentration–time curve, the elimination of half-life, and the relative urinary excretion for 18 major flavonoids (Manach et al., 2005). They found gallic acid and isoflavones to be the best absorbed flavonoids, followed by catechins, flavanones, and quercetin glucosides, but with different kinetics. The least well-absorbed polyphenols are proanthocyanidins, galloylated tea catechins, and anthocyanins. Data were too limited for the assessment of hydroxycinnamic acids and other polyphenols. As a result of digestive and hepatic activity, the metabolites present in blood usually differ from the parent compounds. Depending on the flavonoid, plasma concentrations of total metabolites ranged from 0 to 4 $\mu mol \cdot L^{-1}$ from an intake of 50 mg aglycone equivalents, and the relative urinary excretion ranged from 0.3 to 43% of the ingested dose.

Intervention studies have indicated the type and magnitude of effects among humans in vivo, on the basis of short-term changes in biomarkers. A review of 93 such studies led workers to conclude that flavonoids have varying physiological effects (Williamson and Manach, 2005). They propose that isoflavones (i.e., genistein and daidzein) have weak hormonal effects, but significant ones on processes affecting bone health in postmenopausal women. Monomeric catechins, which occur in exceptional amounts in tea, influence energy metabolism as well as plasma antioxidant biomarkers. Proanthocyanidins, which are widely distributed in many foods, red wine, and supplements such as Pycnogenol (http://www.pycnogenol.com), have pronounced effects on the vasculature that are not limited to antioxidant activity. Quercetin, the principal flavonol in plant-based foods, red wine, and Ginkgo supplements, appears to influence certain markers of carcinogenesis and exerts small effects in vivo on plasma antioxidant biomarkers; nonetheless, some studies failed to corroborate those findings. In fact, the largest randomized, double-blind, placebo-controlled clinical trial ever conducted on a botanical medicine failed to show that extracts of *Ginkgo biloba* L. prevented dementia. Five academic medical centers in the United States between 2000 and 2008 evaluated 3069 community volunteers aged 75 years or older with normal cognition ($n = 2587$) or MCI (mild cognitive impairment; $n = 482$) (Dekosky et al., 2008). Proponents of Ginkgo may argue that this study does not undermine what has already been observed with regard to the usefulness of Ginkgo extract in providing symptomatic relief in persons who already suffer from dementia or Alzheimer's disease or prevent progression in younger, middle-age subjects.

Other workers have found an apparent lack of correlation between the effectiveness of anthocyanins, such as those derived from *Vaccinium*, in laboratory model systems and in humans, especially as cancer chemopreventive agents, as evidenced by epidemiological studies, further illustrating the importance of study design (Wang and Stoner, 2008). A discrepancy exists in the antioxidant and other bioactivities of flavonoids, which are powerful in assays conducted in vitro; the

measured in vivo activities are far more subtle. The reasons for incongruity are cited as (1) lack of validated in vivo biomarkers, especially in the area of carcinogenesis; (2) lack of understanding or consideration of bioavailability and the inherent complexity of flavonoid interactions in the in vitro experiments, which are subsequently used for the design of in vivo studies; and (3) lack of long-term observations. In the design of in vitro and in vivo studies, these issues mandate careful consideration. The length of human intervention studies should be increased, particularly to more closely reflect the consequences of long-term dietary consumption of flavonoids.

The Physicians Desk Reference (PDR) for Herbal Medicines is an authoritative source for efficacy and safety guidelines regarding phytotherapeutics and plant-based dietary supplements (Gruenwald et al., 2007). Although PDR does not endorse specific brands, a select few have contributed indirectly to its content through academic and independent citations therein. PDR employs a consistent format for reporting data, and the categories mirror those for FDA-approved prescription pharmaceuticals. The basic data include a plant's common name and Latin binomial. A description section follows and specifies the medicinal part(s), botanical characteristics, and features of the flower and fruit, leaves, stems and roots, habitat, production, and alternative (common) names. Next is a section on actions and pharmacology that lists known compounds present in the medicinal parts, with a subsection on effects. Clinical trials, if available, comprise the third section, followed by six sections that encompass indications and usage (segregated by approved and unproven uses), contraindications, precautions and adverse reactions, drug interactions, dosage, and, lastly, supporting literature citations.

Three *Vaccinium* species presented in the PDR include *V. myrtillus* (European bilberry), *V. macrocarpon* (cranberry), and *V. uliginosum* (bog bilberry). The PDR cites their beneficial effects but, notably, these presumably innocuous fruits also possess clear risks. *V. myrtillus*is contraindicated during pregnancy and should not be used while breastfeeding, whereas *V. macrocarpon* is contraindicated for use in patients with aspirin allergy, atrophic gastritis, diabetes (when product, such as juice, is sweetened with sugar), hypochlorhydria, and kidney stones. Use of the latter during pregnancy has been reviewed, in light of possible mitigation against elevated risk of urinary tract infections associated with this condition, and no adverse events came to light in a survey of 400 women (Dugoua et al., 2008). Alternatively, no evidence is available for safety during lactation. Although contraindications are not cited for *V. uliginosum*, an overdosage warning is given for signs of poisoning after consumption of large quantities and includes nausea, vomiting, states of intoxication, feelings of weakness, and visual disorders. Presumably, these untoward effects may be traced back to natural contamination of the fruit by a fungus.

Precautions and adverse reactions for *V. myrtillus* include side effects relating to the skin, gastrointestinal tract, and nervous system. Digestive complaints, including nausea, are due to the substantive tannin content of the fruit. High doses and prolonged use may lead to chronic intoxication; chronic administration to animals ($1.5\ g{\cdot}kg^{-1}$ per day minimum) has been reported to be fatal. *V. macrocarpon*is generally well tolerated, but high doses may also cause gastrointestinal upset and diarrhea. Since scientific evidence is not available for use during pregnancy, precaution

rather than contraindication is considered prudent. Side effects of *V. uliginosum* have not been observed in conjunction with proper administration of designated therapeutic dosages.

Drug interactions are some of the most serious considerations associated with *Vaccinium* preparations and supplements. *V. myrtillus* is considered a "moderate risk" when used with anticoagulants, antiplatelet and antithrombotic agents, and low-molecular-weight heparins. Clinical management requires close monitoring for signs and symptoms of bleeding with adjustment of anticoagulant dose if the patient regularly takes a consistent and standardized product. *V. macrocarpon* is considered a "high risk" for bleeding when used in conjunction with warfarin and clinic management involves discouraging patients from excessive use of these products. *V. macrocarpon* is a moderate risk when used with histamine$_2$-receptor antagonist (H_2 blocker) medications that are used to treat heartburn, gastroesophageal reflux disease, and ulcers. H_2 blockers and concomitant use may reduce effectiveness of the drug. Patients taking H_2 blockers should avoid regular consumption of these extracts or juice, although occasional use is probably not harmful. Caution is also prudent for patients taking H_2 blockers because the effect of *V. macrocarpon* extracts on gastric acids is not known. Furthermore, *V. macrocarpon* supplements may result in reduced effectiveness of gastric proton pump inhibitors with concurrent use and requires similar clinical management as for H_2 blockers. *V. uliginosum* may be anticipated to have similar interactions with anticoagulants or gastrointestinal drugs at very high doses, but no report of such effects is published in the literature.

Health-conscious consumers and medical practitioners must be careful about excessive intake of *Vaccinium* extracts and other dosage forms for additional reasons cited in the scientific literature. Their proposed use as anticarcinogens, and cardioprotective and neuroprotective agents, has prompted a dramatic increase in their consumption as dietary supplements (Skibola and Smith, 2000). Despite the fact that flavonoid preparations, many of which derive from *Vaccinium*, are marketed as herbal medicines or dietary supplements for a variety of alleged nontoxic therapeutic effects, most have yet to pass controlled clinical trials for efficacy (Galati and O'Brien, 2004). Although most of the work done to date indicates a chemopreventive activity of these compounds, some studies show cancer-inducing or no effects. Current knowledge about flavonoid toxicity, albeit limited, relates to potential dietary flavonoid/phenolic-induced adverse events, including their pro-oxidant activity, mitochondrial toxicity, and interactions with drug-metabolizing enzymes. The chemopreventive activity observed in animal experiments may result from their ability to inhibit phase I and induce phase II carcinogen metabolizing enzymes that initiate carcinogenesis. They also inhibit the promotion stage of carcinogenesis by inhibiting oxygen radical-forming enzymes, those acting as ATP mimics and inhibitors of protein kinases that contribute to proliferative signal transduction enzymes, and others that contribute to DNA synthesis. Finally, they may prevent tumor development by inducing tumor cell apoptosis by inhibiting DNA topoisomerase II and p53 downregulation but, at the same time, potentially elicit mitochondrial DNA apoptosis. While most flavonoids/phenolics indeed are considered safe,

flavonoid/phenolic therapy or chemopreventive use needs to be assessed carefully, as there have been reports of toxic flavonoid–drug interactions, contact dermatitis, hemolytic anemia, liver failure, and estrogenic-related concerns such as breast cancer and male reproductive health associated with dietary flavonoid/phenolic exposures. At higher doses, flavonoids may act as mutagens, pro-oxidants that generate free radicals, and as inhibitors of key enzymes involved in hormone metabolism. Phenolic acids, anthocyanins, stilbenes, catechins, and other flavonoids have documented effects on the cytochrome P-450 system (Rodeiro et al., 2008). There are several common mechanisms by which these chemicals exert their effects that could be conducive to additive, synergistic, or antagonistic interactions (Nichenametla et al., 2006). Since flavonoids readily cross the placenta, the unborn fetus may be especially at risk. Thus, the adverse effects of flavonoids may outweigh their beneficial ones at high doses. These high levels are above those typically obtained from a balanced vegetarian diet.

There are many different kinds of risks associated with herbal preparations, as delineated in the chapter "Abstract." We document many of these risks in case studies on herbal preparations of ephedra, kava kava, and *Vaccinium*. It turns out that the most serious risks are those associated with adverse interactions that can occur between herbal preparations and pharmaceutical prescription drugs (Table 14.1).

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