INTRODUCTION AND BACKGROUND

Medicinal plants have been used therapeutically throughout the world as tools of traditional medicine, from Ayurveda to Chinese traditional medicine. In western countries, despite the development and production of synthetic medicines, the popularity of over the counter health foods, nutraceuticals, and medicinal products from plants or any other natural source has recently increased because of the belief that they could be more effective than conventional therapies for preventing or treating diseases. This attitude indirectly indicates the lack of confidence of the general public in conventional medical treatments.

Several reasons may account for the worldwide growing use of nutraceuticals and dietary supplements, among them being the lower rate of adverse effects as compared to conventional drugs and the higher costs of many traditional pharmaceutical formulations (Meena et al., 2010; Rao et al., 2011; Martínez-Domínguez et al., 2014).

Consumers increasingly rely on dietary supplements to maintain mental acuity and to overcome age-related problems, such as menopause, benign prostate hypertrophy, and elevated blood pressure and cholesterol levels, and also to relieve stress (Raman et al., 2004).

The term nutraceutical was coined by DeFelice to define any substance that may be considered a food or part of a food providing medical or health benefits. Nutraceuticals may be useful for the prevention and treatment of disease or as an alternative to conventional medicine in primary health care. They include herbal medicines (Ayurvedic, Chinese, Tibetan, African, Amazonian, Herbalism), naturopathy, vitamin and mineral therapy, and homeopathy. Nutraceuticals and food ingredients (NFI) consist of dietary supplements (e.g., vitamins, minerals, co-enzyme Q, carnitine), herbal products (e.g., flavonoids, Ginseng, Ginkgo biloba, Saint John’s wort, Saw Palmetto), and bioengineered and processed foods (e.g., probiotics, omega-3, fish oil, transgenic plants) purported to benefit health (DeFelice, 1995; Pirotta et al., 2000; NNC, 2014).

Lockwood (2007) defines nutraceutical as a term used to describe a medicinal or nutritional component that includes a food, plant, or naturally occurring material that may have been purified or concentrated and that is used for the improvement of health by preventing or treating a disease. Dolan et al. (2003) considered the term “dietary supplement” to describe a product that contains one or more of the following ingredients: vitamins; minerals; herbs or other botanicals, amino acids; dietary substances used as diet supplements to increase the total daily intake; or concentrates, metabolites, constituents, extracts, or combinations of these ingredients. The Dietary Supplement Health and Education Act (DSHEA) defines nutraceuticals as a dietary supplement that may contain an herb or other botanical, or a concentrate, metabolite, constituent, extract, or combination of any ingredient from the other categories (Frankos et al., 2010). However, toxic contamination of NFI during any stage of production can lead to changes in their quality and safety. The health hazard of these products largely depends on the presence of unusually high concentrations of chemical ingredients that may result in toxicity or even fatality if they are consumed (Chan, 2003).

Furthermore, the consumption of NFI contaminated with environmental pollutants by vulnerable subgroups of the population, such as pregnant women, children, and elderly adults may become a serious problem if the tolerable level of exposure is exceeded. For example,
children and toddlers have greater susceptibility to poisoning by heavy metals and metalloids, as opposed to adults because of their lower body weight, resulting in higher dosage of these substances.

Risk assessment paradigms might underestimate the effects of these chemicals on children and the elderly (Gomez et al., 2007). For instance, these subpopulations may be more susceptible to adverse effects associated with ingestion of low doses of heavy metals found in Hypericum perforatum, commonly known as St. John’s wort, widely used for the treatment of mild to moderate forms of depression. Herbal remedies are also frequently used by pregnant women regardless of the scarce information about their safety during pregnancy and breastfeeding. In addition to the risk of miscarriage from several herbs (e.g., nettle, passionflower, and aloe), a number of epidemiologic studies suggest that certain herbs (e.g., those rich in unsaturated pyrrolizidine alkaloids) are associated with embryotoxic or fetotoxic effects (de Smet, 2002; Gurib-Fakim, 2006; Rodriguez-Fragoso et al., 2008).

Because potential interactions between pharmaceutical formulations and herbal products (or other NFI) cannot always be predicted, unexpected effects can be observed because of a change in the magnitude of the effect of conventional drugs (Shaw et al., 1997). These types of interactions can be of either a pharmacokinetic or a pharmacodynamic nature (Rodriguez-Fragoso et al., 2008). One of the most important pharmacokinetic interactions occurs between herbal products and drug-metabolizing enzyme systems, particularly the cytochrome P450 (CYP450) isoenzymes. This type of interaction has great importance in clinical practice because CYP450 isoenzymes metabolize a large number of drugs and chemicals. Also, important genetic polymorphisms of CYP450s have been reported to modify drug disposition in different populations. For instance, the interaction between peppermint oil and some CYP450 isoforms (CYP1A2, CYP2C19, CYP2C9, and CYP3A4) may modify levels of drugs metabolized by these isoforms (Maniacal and Wanwimolruk, 2001; Unger and Frank, 2004).

Good manufacturing practices (GMP) and other legal requirements must be met to avoid adverse reactions or product quality deficiencies as a consequence of the rapid growth of health-related foods and supplements (Genuis et al., 2012).

In the United States, the DSHEA establishes regulations and limits label claims on dietary supplements. In Europe, food supplements are converged by the Directive 2002/46/EC and herbal medicinal products are converged by Directive 2004/27/EC. However, there is no formal legislation regulating nutraceutical products (Gulati and Berry Ottaway, 2006; Martinez-Dominguez et al., 2014). Although conditions for importation of pharmaceutical products are rigorous, the guidelines for importation of certain NFI, including herbal medicines and raw herbs, are quite general and only related to microbiological properties and registration of items themselves. In turn, there are no specific guidelines for active constituents or toxic contaminants (Cooper et al., 2007).

Little information is available on the toxic contamination of nutraceuticals and dietary supplements except for herbal drugs. Hence, this review is based largely on medicinal plants, assuming that they comprise the majority of NFI.

Herbs can be collected indiscriminately from non-cultivated and nonenvironmentally friendly areas by untrained people and placed into the market without any control. This means that consumers might be exposed to herbal products potentially contaminated with pesticides, heavy metals and metalloids, mycotoxins, or radioactivity, or adulterated with drugs (Figure 58.1). The presence of forbidden pesticides or excessive amounts of regulated pesticides and heavy metals depends on the source of herbal materials and whether or not they are grown in a contaminated area. Moreover, chemical toxins may come from unfavorable or wrong storage conditions or chemical treatment during their storage. In turn, the presence of drugs could be related to unprofessional practices of manufacturers. Ideally, the consumption of NFI products should be strictly controlled and is pertinent to better knowledge of the levels of different contaminants (specifically heavy metals and pesticides) in raw materials (Chan, 2003; Meena et al., 2010; Harris et al., 2011).

Phytotherapy has a very long tradition and has been popular for centuries. Medicinal plants have a long history of therapeutic use throughout the world and still constitute an important part of traditional medicine. In the last quarter of the past century, the therapeutic use of herbal products has increased in developed countries.

![FIGURE 58.1](image-url) Main toxic contaminants in nutraceuticals and food ingredients.
because of their popularity among consumers and the widespread opinion that “natural products” implies “harmless products” and the lack of toxic effects. Their easy accessibility and relatively low cost also have contributed to an increased use; however, their popularity and global expansion have raised concerns about the safety and quality of herbal products for public health (Arpadjan et al., 2008; Kosalec et al., 2009).

Consumers are increasingly careful in choosing components for their diet and intend to incorporate high nutrient levels into their standard diet, preferably from natural sources such as plants (Bhat et al., 2010). The increased scientific interest and consumer demand have promoted the development of herbal products such as NFI. Medicinal plants behave as authentic medicines because the chemical substances of which they are formed can have a biological activity in humans. For example, because phenolic acid and flavonoids are natural antioxidants and free radical scavengers, there is a growing interest in their pharmacological applications (Choudhury et al., 2006).

In many countries traditional herbal preparations can be sold on the market as food supplements, which do not require prior safety evaluation. The safety and benefit of plant products are directly related to the quality of the raw materials from which they are derived (Salgueiro et al., 2010).

Herbal medicines are widely used in the United States, with approximately one-quarter of adults reporting their use for the treatment of a medical illness. Herbs are considered dietary supplements in the United States and therefore are subjected to a very limited form of regulation and oversight. Although herbs are often believed to be safe, many side effects have been reported, including direct toxic effects, allergic reactions, toxicity from contaminants, and interactions with drugs and other herbs (Bent and Ko, 2004). Other adverse effects include possible mutagenicity and mistaken plant identities (Ernst, 1998). For instance, liver problems have been reported following the use of Chinese herbal medicine for skin disorders, there have been allergic reactions to royal jelly and propolis, and heavy metal poisoning was found in the Indian subcontinent from Ayurvedic remedies contaminated with these compounds (Shaw et al., 1997).

Overall, adverse effects of herbal drugs can be divided into two main groups: intrinsic and extrinsic. The former includes predictable toxicity, overdose, pharmacological interactions, idiosyncratic reactions (e.g., allergy and anaphylaxis), and delayed effects such as carcinogenicity and teratogenicity. The extrinsic undesirable effects largely involve the quality of the herbal medicinal products, which can be challenged by substitution, adulteration, contamination, misidentification, lack of standardization, and inappropriate labeling (Koh and Woo, 2000; Mazzanti et al., 2008; Rao et al., 2011).

Although raw materials are typically and supposedly free of substances that are currently added to patent medicines, they could contain relatively low levels of toxic compounds, particularly heavy metals and pesticides. The majority (>95%) of the samples analyzed by Harris et al. (2011) contained concentrations of heavy metals or pesticide residues that were considered of negligible concern. Nevertheless, the elevated number of samples showing detectable levels of contaminants makes it advisable to monitor the concentration of heavy metals (especially cadmium and chromium) and pesticide residues (especially organophosphorus and organochlorine compounds) in raw materials.

However, if medicinal plants are used for infusion preparations, then the extractable component of toxic compounds would only be available for consumers. In this case, the concentration of contaminants (e.g., heavy metals) dissolved in the infusions should usually be below safety levels for human consumption (Kainy et al., 2007).

### CHEMICAL CONTAMINATION IN NUTRACEUTICALS AND FOOD INGREDIENTS

#### Heavy Metals, Metalloids, and Oligoelements

The sources of environmental pollution from heavy metals are quite diverse and mainly consist of industrial and traffic emissions, agricultural effluents, batteries containing cadmium, organic mercury fungicides, and lead arsenate as an insecticide. The concentration of these contaminants in ecosystems has increased in past decades as a result of anthropogenic activities. Because of the intrinsic toxicity of heavy metals, their presence in the environment may pose a potential threat to terrestrial and aquatic biota. In fact, metal pollution adversely affects the density and diversity of biotic communities, including human (Gomez et al., 2007).

The content of essential and trace elements in medicinal plants vary depending on various factors (Haider et al., 2004). Among these factors are geoclimatic conditions, geochemical characteristics of the soil, anthropogenic activities (e.g., chemical industries in the vicinity), plant species (some can selectively accumulate toxic elements), and the part of the plant used for preparing the herbal medicine. The level to which metals accumulate in plants is also influenced by the physicochemical properties of the soil where plants grow (characteristics of soil or sediments, pH level, exposure period, dispersion range, and presence or absence of other elements). These properties determine the nature of the association of trace elements with soil components and are key elements for the bioavailability of metal elements.
(Sarma et al., 2011). While plants readily assimilate trace elements through the roots, these compounds can also be absorbed through the leaves. Rainfall, atmospheric dusts, plant protection agents, and fertilizers are additional sources of trace elements for plants (Łozak et al., 2002). Although some trace metals present in foods play a physiological role as essential compounds and cofactors, contamination or adulteration of NFI with heavy metals, metalloids, and mineral nutrients (Table 58.1) is a matter of concern. Although lower concentrations of trace elements have health benefits, higher levels may pose health risks (Bhat et al., 2010). Because of their cumulative properties and toxicity, heavy metal concentrations could reach levels potentially leading to hazardous effects on human health.

Cadmium (Cd), mercury (Hg), lead (Pb), and arsenic (As) are nonessential toxic elements of special concern because of their toxicity even at low concentrations (Hsu et al., 2006; Rao et al., 2011). Lead exposure has been associated with renal tumors, reduced cognitive development, and increased blood pressure and cardiovascular toxicity. Cd may induce kidney dysfunction, osteomalacia, and reproductive deficiencies. Mercury may cause neurological disorders and kidney damage (Goyer and Clarkson, 2001; Garcia-Rico et al., 2007). Aluminum (Al) can be accumulated in certain tissues and has been associated with serious health problems, such as Alzheimer’s disease (AD), dysfunction of the blood–brain barrier (BBB), and inhibition of hydroxyapatite formation, which may lead to decreased skeletal mineralization (osteopenia) (Rubio et al., 2012). In addition, Pb and Hg may reach and cross the placental barrier and interfere with placental transport systems, thus increasing prenatal exposure to these toxic compounds (Gupta, 2009, 2011). Despite these well-known adverse effects, the interpretation of total metal concentration (e.g., all ionic forms) and toxicity should be based on analytical results for the more toxic form.

The International Agency for Research on Cancer (IARC) has classified certain trace elements (As, Sb, Be, Cd, Cr, Co, Pb, Ni, and V) as potentially carcinogenic to humans because of their potential to induce DNA damage. Thus, it should be noted that it is important to monitor the presence of such metal elements in medicinal plants used as NFI to prevent excessive human exposures (Sarma et al., 2011).

Medicinal plants are good sources of mineral elements (Özcan et al., 2008) and they might be used as food supplements or for food fortification of new NFI with health-promoting properties. Thus, measuring mineral elements and heavy metal concentrations in NFI is important not only from a nutritional point of view but also for the assessment of their quality and safety (Bhat et al., 2010).

In contrast to the extensive research performed on nutrient elements to define their role in the human diet, studies reporting the mineral content of NFI (e.g., spices and herbs) are limited. Malik et al. (2008) reported that infusions of some nontraditional plant species used for the preparation of stimulant beverages could be a valuable source of nutrient elements for the human diet. In particular, because zinc (Zn), copper (Cu), and molybdenum (Mo) are vital for many physiological functions, their intake is considered good for human health. Zinc acts as a catalyst, coactive, or structural unit for some enzymes and is a cofactor of metalloenzymes. Zinc deficiency can impair normal growth and development, reproduction, and immune function. Copper acts as a cofactor in cuproenzymes, which are essential enzymes for normal functioning of the body. Molybdenum is a component of the sulfite oxidase enzyme, a molybdoenzyme that catalyzes the last step in the degradation pathway of sulfur amino acids (Kosalec et al., 2009).

However, these essential metals are toxic above certain thresholds. High supplementation of oligoelements such as Cu or Zn has been related to adverse effects; for example, high Cu levels induce liver damage and high Zn concentrations reduce immune function.

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<th>TABLE 58.1 Toxic Contaminants Reported in Nutraceuticals and Food Ingredients</th>
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<td><strong>Trace metals</strong></td>
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and high-density lipoproteins levels and also produce adverse interactions with Cu. Thus, eating contaminated or adulterated foods that are not considered usual dietary sources of essential compounds may result in an inadvertent overdose, especially because consumers are often recommended to use food supplements as sources of essential elements. Exposure to these compounds from various sources could lead to additive effects as well (Tongesayi et al., 2013).

Although herbal medicines may be as efficient as synthetic drugs for certain health disorders, the presence of unacceptably high levels of heavy metals makes them less safe (Blicharska et al. 2010). Thus, herbal medicines may be responsible for the growing number of cases of adverse health consequences caused by their use (WHO, 2003). Heavy metals have been widely found in raw herbal products (Wong et al., 1993; Rai et al., 2001), and some plant species are known to be heavy metal hyper-accumulators (Pollard et al., 2002). This property has made some plants an effective source for bioaccumulation of heavy metals from contaminated soils (phytoremediation). Thus, the consumption of these plants as food or therapeutic agents in traditional medicine may prove to be hazardous (Barthwal et al., 2008).

Patent herbal medicines (which consist of a mix of different substances in either pill or extract form) may contain intentionally added heavy metals (Saper et al., 2008). This is the case with Ayurvedic traditional herbal preparations, which may contain high levels of metals (Pb, Hg) or metalloids (As) as a result of the intentional incorporation of certain metallic preparations such as lead monoxide, red mercury sulfide, mercurous chloride, red mercury oxide, arsenic sulfide, disulfide or trisulfide, and arsenic trioxide (Martena et al., 2010).

Heavy metal contamination has been well documented and numerous studies have identified traditional medicines containing high levels of toxic heavy metals (Ernst and Thompson Coon, 2001; Dwivedi and Dey, 2002; Caldas and Machado, 2004; Saper et al., 2004; Kauffman et al., 2007; Rai et al., 2007; Meena et al., 2010; Rubio et al., 2012), sometimes exceeding permissible levels for some analyzed species (Sarma et al., 2011).

Toxic amounts of heavy metals in herbal preparations and case reports of heavy metal poisoning from traditional herbal products have been reported in the literature (Ernst, 2002; Tait et al., 2002; van Vonderen et al., 2000; Fuh et al., 2003). The potential severe consequences from side effects of certain herbal products have also been noted (Gurib-Fakim, 2006; Bush et al., 2007).

Trace metal monitoring in herbal products represents an important field of research that continuously provides relevant information for risks assessment and for setting permissible levels (Rubio et al., 2012). One continuing problem in protecting consumers of plant-based medicines is the lack of standardization of permissible levels of trace metals in herbal medicines by regulatory governmental entities (Sarma et al., 2011). The World Health Organization (WHO) has regulated maximum permissible limits of toxic metals like As, Hg, Cd, and Pb in herbal medicines, which amount to 10, 1.0, 0.3, and 10 ppm, respectively (WHO, 1998). However, the WHO has not set permissible limits for essential metals because many of them are considered micronutrients. Rai et al. (2007) analyzed herbal formulations for Pb and Cd, and results were within the aforementioned permissible limits. Markert (1994) reported the normal Cr, Mn, and Zn compositions of plants, which were 1.5, 200, and 50 ppm, respectively.

The United States has standardized recommended daily dietary allowances (RDA) for essential dietary trace elements, but not for toxic metals (Sarma et al., 2011). In Europe, the European Commission discussed the need for setting maximum levels of Pb, Cd, and Hg in food supplements to amend the Commission Regulation (EC) No. 1881/2006, because monitoring studies found high levels of these metals in certain food supplements. The following limits were then set: 3.0 mg/kg for Pb; 1.0 mg/kg for Cd (except for seaweed products, where the limit was set at 3.0 mg/kg); and 0.10 mg/kg for Hg (Commission Regulation EC No. 629/2008; Gasser et al., 2009).

In 2009, the WHO and the Food and Agriculture Organization (FAO) jointly proposed acceptable levels for toxic substances that can be ingested on a weekly basis—the Provisional Tolerable Weekly Intake (PTWI). The following PTWI levels were set: Cd (7 μg/1,500 μg/person); Pb (25 μg; 1,500 μg/person); inorganic As (15 μg; 900 μg/person); and Hg (5 μg; 300 μg/person) (JECFA, 1988, 1999, 2005).

Few reports have addressed metal intakes from dietary supplements. A limited study on the safety of the botanical dietary supplements (Echinacea, garlic, G. biloba, ginseng, grape seed extract, kava kava, S. palmetto, and St. John’s wort) evaluated the presence of undesired heavy metals and did not find unacceptable concentrations that might pose a health risk to consumers, including pregnant women and children (Raman et al. 2004). García-Rico et al. (2007) investigated the presence of Cu, Zn, Cd, Pb, and Hg in dietary supplements and the estimated daily intakes were below those recommended by WHO (1989), thus suggesting that little intake of metals is associated with the consumption of dietary supplements. However, daily intake of certain metals, like Pb, might increase due to the number of consumed dietary supplements, so the intake of combined supplements plus fortified foods may be a cause for health concern.

Cooper et al. (2007) found that certain traditional Chinese medicines (TCMs) were severely contaminated with As, Pb, and Hg. This unacceptable finding can place consumers at risk for severe or even fatal heavy metal/metalloid poisoning from the consumption of these...
natural therapies. However, the calculated dose of heavy metals/metalloids ingestion from these products is expected to be lower if their bioavailability is less than 100%. Thus, the risk assessment of nonprescription medicines or supplements needs to consider data on bioavailability to ensure that future guidelines are achievable and efficient in preventing undue intake of dangerous ingredients.

The importance of good quality control for medicinal herbs to protect consumers from heavy metals contamination should be emphasized (Başgel and Erdemoglu, 2006). The estimation of trace metal residues in nutraceuticals and food formulations should be mandatory for pharmaceuticals and food ingredients to assure consumers of their quality.

Pesticides

Pesticides are among the most widely used chemicals in the world, and are also one of the most dangerous contaminants to humans. The application of pesticides in modern cultivation becomes indispensable for a growing demand of quantity and quality in products, particularly to increase crop productivity and minimize any possible loss due to uncontrollable pests.

Exposure to pesticide residues can result in many different adverse health consequences, from acute problems such as skin rashes and asthma attacks to chronic problems including cancer, neurological, reproductive, and respiratory disorders (Zuin and Vilegas, 2000; Calvert et al., 2004; Leung et al., 2005; Parrón et al., 2011, 2014).

Consumers of medicinal plants expect these herbs to be produced under good agriculture practices, with no residues of environmental pollutants, including pesticides. However, pesticides are often used to improve the production of Chinese medicinal plants, and thus the presence of pesticide residues in these materials become pitfalls for safety (Qing et al., 2009). Therefore, it becomes absolutely essential to ensure the quality of medicinal plants and to detect the potential presence of pesticides (Table 58.1). However, analyses of crude herbal materials have often shown the presence of pesticide residues. High levels of pesticide residues in medicinal plants can impact the marketing of these products, especially those prepared for exports, because regulations in most of the importing countries are very strict. Nevertheless, in practice, the large-scale cultivation of medicinal and food plants is not possible without using pesticides (Ahmed et al., 2001; Sarkhail et al., 2012).

According to chemical structure, pesticides are classified as organophosphorus (OP) pesticides (e.g., chlorpyrifos and methylchlorpyrifos, coumaphos, dichlorvos, ethion, fenchlorphos, malathion, parathion), organochlorine (OC) pesticides (e.g., hexachlorocyclohexanes [HCH], lindane, dichlorodiphenyl trichloroethane [DDT]), nitrogen-containing pesticides (e.g., atrazine), and pesticides of plant origin (e.g., pyrethroids and rotenoids) (Kosalec et al., 2009).

Although the use of pesticides contributes to productivity and higher agricultural yield, there is growing concern about their adverse effects on human health. Because of their lipophilicity, OP insecticides are readily absorbed through ingestion, dermal absorption, or inhalation. Although their primary toxicity results from acetylcholinesterase (AChE) inhibition in neural tissue, OPs, carbamate, and OC pesticides can also induce cellular oxidative stress via affecting mitochondrial function and may disrupt the neuronal and hormonal status of the body (Karami-Mohajeri and Abdollahi, 2011; Sarkhail et al., 2012; Gupta and Milatovic, 2012; Milatovic et al., 2013; Gupta et al., 2015).

Unfortunately, incidents concerning relatively high levels of pesticide residues have repeatedly been found in herbs exported from different countries (Leung et al., 2005). Residues of malathion, dimethoate, chlorpyrifos, and propenophos have been reported in medicinal herbs from Egypt, with malathion being the OP insecticide most often detected (Ahmed et al., 2001). Malathion, followed by profenofos, was also the OP most frequently found in leafy vegetables and some aromatic medicinal plants collected from different areas of Egypt (Dogheim et al., 2004). Residues of malathion and diazinon have also been reported in herbal drugs from Iran (Sarkhail et al., 2012). The relatively high occurrence of malathion residues may be accounted for by the fact that it is usually the recommended pesticide to be used on medicinal plants worldwide (Ahmed et al., 2001).

Although OC pesticides possess comparatively long residual actions, most of them are now banned because of their low biodegradability and persistence in the environment, where they can be detected for long periods of time. These pesticides also show long-term toxicity, particularly cancer and endocrine disruption potential (Mnif et al., 2011).

Xue et al. (2008) analyzed different TCMs for OC pesticides, and those most commonly found were benzene hexachloride (α-BHC), pentachloronitrobenzene (PCNB), hexachlorobenzene, and tecnazene. Approximately three-quarters (75.8%) of the herbal medicines studied by these authors contained at least one OC insecticide, and more than 50% of samples contained two of them. Nevertheless, their concentration was below the MRLs set in the regulatory Pharmacopeia.

Quintozene, endosulfan, and BHC were the pesticide residues most commonly detected in ginseng products (Sohn et al., 2004). Despite DDT series and γ-BHC being pesticides frequently encountered in Chinese herbal medicinal products, their concentrations were, in general, below the allowable limits set by different countries (Wong et al., 2007).
Harris et al. (2011) analyzed pesticide content in commonly prescribed individual raw Chinese herbal medicines and reported the following proportion of samples with an elevated level of background pesticide exposure: 26% for chlorpyrifos; 1.4% for methyl-parathion; and 0.3% for esfenvalerate, fenvalerate, fipronil, lindane, and quintozene. Overall, pesticides most often found in Chinese herbal products include BHC, DDT, and PCNB, with pyrethroids and aminofluorins rarely being found. Among the potentially polluting pyrethroids, attention has been focused on permethrin and cypermethrin (Qing et al., 2009). In contrast, there are also studies in which residues of OC, OP, and pyrethroid pesticides have not been detected in any herbal medicinal plants (Rao et al., 2011).

Residues of hexachlorocyclohexane (HCH) isomers and metabolites have been detected in some herbal Ayurvedic formulations (Rai et al., 2007). Although some DDT metabolites were also found, HCH concentrations were comparatively higher than those of DDT. γ-HCH was the HCH isomer found in the greatest concentrations in all samples, as it is one of the more persistent isomers. Rai et al. (2008) also reported the presence of total HCH and its isomers in “Dashmoola,” a popular Ayurvedic herbal formulation with immunomodulatory and febrifugal properties. α-HCH and γ-HCH, the main constituents of commercial HCH formulations, were detected in 97.5% samples, with γ-HCH being more prominent in comparison to the rest of the isomers. Only 5% of the samples contained DDT (or metabolites) residues. These findings indicate that residual HCH build-up is more prevalent in plant samples than DDT.

With regard to nutraceuticals other than herbal medicines, residues of HCB, HCH isomers, and DDT as well as polychlorinated biphenyls (PCBs) have been found in cod liver oil used as a dietary supplement (Storelli et al., 2004). HCB contributed very little to the overall contaminant burden of dietary supplement oils, whereas HCH isomers were generally below instrument detection limits (Bengtson Nash et al., 2014). In light of these findings, and considering that these and other persistent organic contaminants are accumulated in the lipid stores of organisms from marine ecosystems, there is a need for strict and continuous monitoring of their content in fish and krill oil products to reduce as much as possible the risks for human health (Bengtson Nash et al., 2014).

Mycotoxins

Mycotoxins are secondary metabolites produced by fungi that are capable of causing toxicity and even death in humans. They are low-molecular-weight toxic metabolites produced by molds that can contaminate medicinal herbs and their preparations and products. Mycotoxin production depends on several factors, including genetic features, substrate, humidity, CO₂/O₂ ratio, and the presence of fungicides or other competitive microbial species (Kosalec et al., 2009; Martins et al., 2001).

Although the presence of toxicogenic molds in an herbal plant does not imply the presence of mycotoxins in the product, it represents a potential risk of contamination with mycotoxins. Microbiological and mycotoxico-cological quality assessment of medicinal herbs should include mycotoxin contamination (Table 58.1), especially of herbs grown in hot and humid climates, and in the herbal parts showing higher risk of contamination (Kabelitz and Sievers, 2004).

Raman et al. (2004) evaluated several botanical supplements and found the presence of molds in a great number of samples. The most frequently isolated molds in medicinal plants were Penicillium sp., Aspergillus niger, and Fusarium sp. (Abou-Arab et al., 1999). Packed samples of medicinal plants have a higher probability of being infected with molds than nonpacked samples, because of the increased humidity inside the pack and unsuitable storage methods.

A number of studies have reported the presence of mycotoxins in herbal products. Bugno et al. (2006) studied medicinal herbs collected from a Brazilian market and found molds of the Aspergillus and Penicillium genera to be the most common contaminants of raw medicinal herbs. Santos et al. (2009) found that all the analyzed medicinal herb samples collected in Spain were contaminated with several mycotoxins, and nearly 87% showed the combination of four or more mycotoxins.

However, Romagnoli et al. (2007) studied aflatoxin B1 contamination in different kinds of spices, aromatic herbs, and medicinal plants from Italy, and none of the plants analyzed showed detectable levels of aflatoxins. Aflatoxin B1 is the most common and toxic metabolite produced by Aspergillus flavus, and its toxic effects include immunosuppressive, mutagenic, teratogenic, and hepatocarcinogenic activity (Prado et al., 2012).

The European legislation has set maximum levels of certain mycotoxins (aflatoxin B1 and the sum of B₂, B₁, G₁, and G₂) for a variety of foodstuffs and spices. The European Pharmacopeia has also provided a limit of 2 µg/kg for aflatoxin B1 and 4 µg/kg for the sum of aflatoxins B₁, B₂, G₁, and G₂ for some medicinal herbs. For ochratoxin A (OTA), a limit of 20 µg/kg has been adopted in liquorice root (Glycyrrhiza glabra) (Commission Regulation EC No 472/2002; EDQM Chapters 2.8.18 and 2.8.22, 2007a,b).

OTA is a mycotoxin with nephrotoxic, hepatotoxic, embryotoxic, teratogenic, neurotoxic, immunotoxic, genotoxic, and carcinogenic properties. It is a secondary low-molecular-weight metabolite produced by some fungal species, notably Penicillium verrucosum and Aspergillus ochraceus, and to a lesser extent Aspergillus
carbonarius and Aspergillus niger. All these mold species can contaminate medicinal herbs with OTA, particularly in temperate and colder zones (Pitt, 2000; Ostry et al., 2013).

Fumonisins are mycotoxins mainly produced by Fusarium verticillioides (F. moniliforme) and Fusarium proliferatum, with the most abundant being fumonisin B₁ (FB₁), which is considered as possibly carcinogenic (class 2B). Only a few studies have investigated FB₁ contamination of medicinal herbs and herbal products. Omurtag and Yazicioglu (2004) measured the potential levels of FB₁ contamination in herbal teas and medicinal plants that are consumed regularly in Turkey. FB₁ was detected in two samples (0.160 and 1.487 μg/g). Sewram et al. (2006) investigated the presence of FB₁ in 19 dietary and 30 medicinal wild plants used by residents of Eastern South Africa. Eight plants, four dietary and four medicinal, were positive for FB₁ at levels ranging from 34 to 524 μg/kg and from 8 to 1,553 μg/kg, respectively.

Citrinin is another mycotoxin produced by Monascus sp. (M. purpureus, M. ruber) and Penicillium sp. (P. citrinum, P. expansum, P. radicicola, and P. verrucosum). Although this mycotoxin has a powerful nephrotoxic effect, it is devoid of mutagenic and carcinogenic potential. Citrinin has been found in foodstuffs of vegetable origin (e.g., cereals, pomaceous fruits, black olive, roasted nuts, spices), food supplements based on rice fermented with the red microfungi Monascus purpureus, and in foodstuffs of animal origin (e.g., cheese) (Ostry et al., 2013). Monascus-fermented rice has recently become a popular dietary supplement to reduce serum cholesterol level because many of its bioactive constituents, particularly monacolins, are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. However, controversy about its safety has been raised because citrinin is produced along with the Monascus secondary metabolites by certain strains or under certain cultivation conditions (Lin et al., 2008).

Radioactive Contamination of Nutraceuticals and Food Ingredients

Mushrooms are a good source of digestible proteins and fiber, are low in fat and calories, and provide a valuable vitamin and mineral intake. For this reason, there is a growing interest in the use of dried mushroom extracts as NFI for health promotion. Some mushroom species have been shown to lower cholesterol levels, have antioxidant activity, and may modulate mononuclear cell activation and the phenotypic expression of cytokines, thus enhancing the immune system function. Despite these beneficial effects, there are concerns because of the high heavy metal concentrations that may be found in wild edible fungi. These compounds are a known source of chronic poisoning and can also contribute markedly to the contamination with radioactive chemicals such as 137Cs (Table 58.1) (Borchers et al., 2004). Higher radiocesium activity particularly occurs in mycorrhizal species. While most samples of wild edible fungi have detectable levels of radioactive Cs, radiation doses to individuals resulting from edible fungi consumption are dominated by 210Pb (de Román et al., 2006).

Phosphate feed supplements may contribute to the radiation exposure of the population because phosphates usually contain appreciable quantities of uranium (U) and its daughters 238U, 234U, 236Ra, and 210Po (210Pb). The exposure of consumers depends on the degree of equilibrium of the decay chain in the feed and through the metabolic process. Poultry products, particularly chicken meat, organs, and eggs, have shown to be contaminated through poultry feed supplements containing phosphorus (Izak-Biran et al., 1989).

Adulteration and Undeclared Chemical Substances in Nutraceuticals and Food Ingredients

Terms such as “natural,” “herbal,” and “dietary supplement” are sometimes used as a means to mislead consumers, health professionals, and health authorities, and to obscure the potential adulteration of these products with synthetic active compounds (Table 58.1).

Dietary supplements have widespread use in sports, and most athletes competing at the highest levels use some form of dietary supplementation. A number of contaminants have been identified in some supplements, including a variety of anabolic androgenic steroids (e.g., testosterone, nandrolone, and their pro-hormones), ephedrine, and caffeine. While in most cases this contamination comes from poor manufacturing practices, there is some evidence of a deliberate adulteration (Maughan, 2005).

A doping case associated with the use of ephedra-labeled dietary supplement has been reported (Ros et al., 1999), which illustrates that the potential adulteration of herbal food supplements with undeclared agents has to be considered. The predominance of norephedrine over ephedrine indicates deliberate spiking with the former compound. While manufacturers usually meet their labeling claims for ephedra-free products (Tam et al., 2006), special attention should be given to the presence of drugs like caffeine, synephrine, and botanical sources of caffeine because these ingredients have replaced ephedra in some dietary supplements.

Many products labeled “herbal” or “all natural” (herbal/natural) are marketed as over the counter dietary supplements for the treatment of erectile dysfunction.
because they claim to enhance sexual performance. However, adulteration with undeclared phosphodiesterase type 5 inhibitors (e.g., sildenafil and its structurally modified analogs), which have proven efficacy in the treatment of erectile dysfunction, appears to be widespread among the Chinese over the counter medicines labeled for the treatment of sexual dysfunction in men (Campbell et al., 2013).

**Risk Assessment of Toxic Contaminants in Nutraceuticals and Food Ingredients**

The maximum amounts of toxic metals and nonmetals in medicinal plant materials can be given based on the provisional tolerable intake (PTI) values. The limits for toxic metals in herbal medicines and products vary throughout the world. The use of herbal medicinal products is not generally expected to contribute significantly to the exposure of the population to heavy metal contaminants. However, it should be understood that the heavy metal content of herbal medicines adds to the burden originating from food, so it is recommended that heavy metal contamination is minimized (WHO, 2007).

Limits for pesticide residues should be established following the recommendations of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), which includes an acceptable daily intake (ADI) and the analytical methodology for the assessment of pesticide residues. However, there are no standard procedures for assignment of MRLs to medicinal plants. The methodology used for food commodities could be applied when a botanically identical medicinal plant is used as food. If so, then the established MRL for a specific pesticide in the latter could be regarded as the relevant MRL for the specific raw medicinal plant material. The toxicological evaluation of pesticide residues in herbal materials should be based on the likely intake of the material by consumers. In the absence of a full risk assessment, it is recommended that the intake of residues from herbal materials should account for no more than 1% of total intake from all sources (WHO, 2007).

Maximum residue levels (MRL) have been set for food and animal feed by different world organizations, like WHO, the Food and Agriculture Organization (FAO), the US Environmental Protection Agency (EPA), and the European Union (EU). The European Regulation EC 396/2005 defines MRL as the upper legal concentration limit for a pesticide residue in or on food or feed, based on good agricultural practices and the lowest consumer exposure. Because this regulation only concerns raw materials, there is a need to define MRL for NFI to assure the safety of this type of product (Martínez-Dominguez et al., 2014).

Harris et al. (2011) interpreted the toxicological significance of levels of contaminants found in NFI (Figure 58.2) following three different comparisons. First, levels of contaminants were expressed as percent of the reference dose (RfD) or population-adjusted dose (PAD) from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and EPA IRIS (Integrated Risk Information System). Second, concentration of contaminants was also compared with the minimal risk levels (MRLs) provided by the Agency for Toxic Substances and Disease Registry (ATSDR), which are based on toxicological studies in animals and on reports of human occupational exposure. MRL is an estimate of the daily human exposure to a hazardous substance (based on an average body mass of 70 kg) that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. Third, levels of contaminants were also compared with the maximum acceptable concentration limits proposed for dietary supplements from the NSF/ANSI Standard 173 and the European Pharmacopoeia for dried herbal infusions (Harris et al., 2011). Based on the assumptions of the mode of consumption of raw Chinese herbal medicines, the 99% and 95% of samples tested by Harris et al. (2011) for heavy metals and pesticide residues, respectively, were likely to be of negligible concern.

**Concluding Remarks and Future Directions**

The general public as well as health care professionals should be better informed regarding the basic concept of NFI and their usefulness, and should also be warned about the potential adverse effects associated with their use because of the potential of toxic contamination. Because of the increased use of a variety of
alternative remedies, physicians should also be aware of these potential sources of toxic contamination when diagnosing conditions of uncertain etiology that have similarities to toxic syndromes.

Given that many circles foster the use of herbal medicines as an alternative to synthetic pharmaceutical compounds for the prevention and treatment of particular diseases, there is a need for strict guidelines and more concern by the international regulatory legislation (Ahmed et al., 2001). Thus, an appropriate regulatory framework should be developed for medicinal herbs and herbal products to prevent and screen for contamination and to ensure that safety and quality standards are met (Kosalec et al., 2009). Implementation of a regulatory system will require evidence of safety of ingredients, quality assurance (including authentication of herbal ingredients), and encouraging appropriate research on efficacy (Shaw et al., 1997).

Phytomedicinal safety assessments necessarily involve the development of adequate analytical procedures for the analysis of toxic compounds in medicinal plants. These procedures must be implemented by the pharmaceutical industry and official regulatory laboratories as screening protocols to identify heavy metals, pesticides, and mycotoxins in herbal drugs and other NFI (Zuín et al., 2003). In this regard, consumers should be advised to minimize long-term consumption of herbal infusions until data on the levels and varieties of different toxic contaminants are made widely available. Care must be taken to pick medicinal plants from areas free of any contamination source (Manteiga et al., 1997).

If the methods for the correct and appropriate use of medicinal plants are correctly applied, then they can contribute to protecting and improving consumer health and well-being. The correct use of such methods should follow the criteria of safety, efficacy, and quality, which characterize modern medical practice and are the basis for consumer protection.

The efficacy and safety of herbal remedies or food supplements have been assessed by many studies and adverse effects have been reported. These data need to be brought together, along with data collected from adverse reaction monitoring systems, to enable patients and physicians to make the best risk–benefit assessment before using any herbal or traditional medicine. Definitive and greater control over the safety and quality of NFI could be achieved through good manufacturing practice, regulatory control, and research efforts, as well as by reporting of adverse events (Koh and Woo, 2000). Regulators should also take actions to minimize these risks.

Finally, additional research is needed to define the pharmacology, stability, and bioavailability of dietary supplements, including medicinal herbs, to improve the safety and efficacy of these products (Bent and Ko, 2004).

References


