Chapter 21
Chemical Inquiry into Herbal Medicines and Food Additives

Natsuko Kagawa

Abstract Medicinal and aromatic plants are valuable sources of natural products that contribute to human health. Herbal medicines and some food additives are derived from medicinal and aromatic plants, and to prove their safety and efficacy, chemical analyses of the concentrations of active natural compounds in raw plant materials are essential. This chapter discusses the phytochemistry of medicinal and aromatic plants, the chemical requirements for the production of raw plant materials, and the analytical methods used for quality control. Plant factories offer the use of technology that more efficiently enhances the production of targeted compounds by controlling a plant's metabolism and can provide sustainable harvesting of medicinal and aromatic plants, which will conserve valuable source-plant species for future generations.

Keywords Medicinal and aromatic plant · Herbal medicine · Natural product · Bioactive compound · Chemical analysis · Quality concentration · Sustainable harvest · Conservation of source-plant species

21.1 Introduction

Plant factories with artificial lighting (PFALs) have great potential for the cultivation and sustainable harvesting of medicinal and aromatic plants. Phytochemicals produced by these plants are utilized as pharmaceuticals, herbal medicines, food additives, and cosmetics on the world market. To supply these plants as raw materials for industry and to conserve plant species from the threat of over-harvesting, ideas for their cultivation are proliferating. When cultivating medicinal and aromatic plants, however, it is difficult to maintain quality concentrations of phytochemicals. PFALs must develop cultivation methods that will promote both plant growth and chemical accumulation.

N. Kagawa (✉)
Center for Environment, Health and Field Sciences, Chiba University, Kashiwa, Chiba, Japan
e-mail: knatsuko@faculty.chiba-u.jp

T. Kozai (ed.), *Smart Plant Factory*, https://doi.org/10.1007/978-981-13-1065-2_21

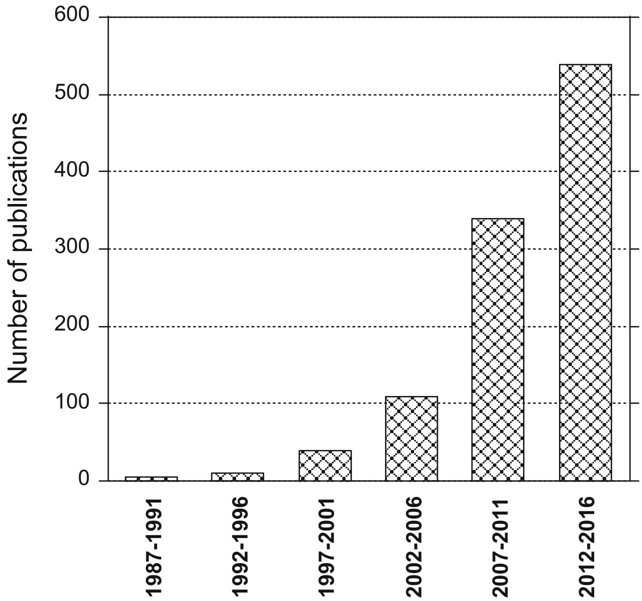


Fig. 21.1 The number of publications in 5-year increments

21.2 Issue of Concern with Medicinal Plants

Global interest in the cultivation of medicinal and aromatic plants is mounting. A survey of the topics of most interest via a search of science websites is revealing. In 5-year increments, Fig. 21.1 tracks the trends in the number of scientific publications that cite both the words "cultivation" and "medicinal plants" as topics that have increased during the past 30 years. In particular, the number of publications listed for the period from 2007 to 2011 reached 339, which is 3 times that of the previous period (2002 to 2006). The number of countries by author affiliation has also increased, and from 2012 to 2016, researchers in more than 100 countries had contributed to studies closely related to the cultivation of medicinal plants.

Figure 21.2 shows another trend whereby the number of research areas in publications related to the cultivation of medicinal plants reached 63 during the latest period (2012 to 2016) and included topics such as plant science, agriculture, pharmacology and pharmacy, biotechnology applied to microbiology, environmental science ecology, chemistry, and food science technology.

Growing pressure to conserve species threatened by over-harvesting is a subplot of these trends. International action is pursuing the achievement of sustainable harvesting since the market for herbal production is worldwide and most countries are involved in the trade of medicinal and aromatic plants as exporting, importing, manufacturing, or consuming countries.

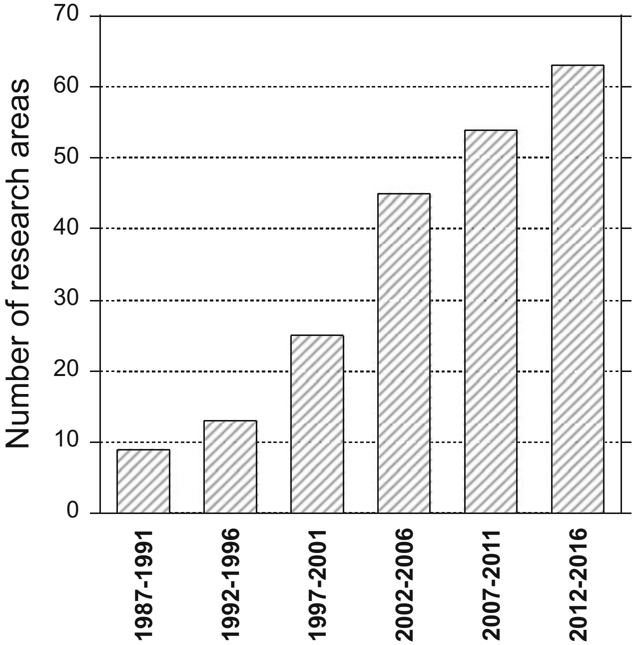


Fig. 21.2 The number of research areas in 5-year increments

21.3 Active Compounds in Herbal Medicines

Medicinal and aromatic plants are used for the production of herbal medicines and food additives. Herbal medicines in Europe are marketed as pharmaceuticals in the form of extracts, teas, tinctures, and capsules obtained from medicinal and aromatic plants (Lubbe and Verpoorte 2011). These are known as botanical drugs in the United States.

In Japan, the raw materials from plants that are used for herbal medicines include traditional medicines such as Kampo, and these are referred to as crude drugs and related drugs in the *Japanese Pharmacopoeia*. Crude drugs and their related products include extracts, powders, tinctures, syrups, spirits, fluidextracts, or suppositories containing crude drugs as the active ingredient and combination preparations containing crude drugs as the principal active ingredient in the *Japanese Pharmacopoeia* (JP17, 2016).

Plants produce compounds that are numerous and diverse and are called natural products, secondary metabolites, phytochemicals, or natural compounds. Plants and their crude extracts are complicated mixtures of compounds and generally contain many hundreds of phytochemicals. Natural compounds in the extracts of medicinal and aromatic plants have been investigated in clinical trials for many herbal medicines for their ability to prevent and treat diseases. In most cases, those efforts have focused on identifying the bioactive compounds that are responsible for the medicinal effects of herbal medicines.

Many people who rely on modern Western scientific medicines tend to prefer a single substance as the most important ingredient in a medicine (Houghton 2001). The active principle concept in medicine is responsible for the progress of modern chemistry, and this has enabled many natural products to be characterized as bioactive molecules when isolated as pure substances from the extracts of medicinal and aromatic plants.

It is important to note that a high percentage of the world's population still uses crude extracts of local plants as traditional medicines, although their bioactive compounds have not been fully elucidated. In contrast to the use of those folk medicines, the use of herbal medicines that are standardized in terms of the active constituents is increasing in industries such as food, cosmetics, and pharmaceuticals.

In the food and cosmetics industries, various constituents extracted from plants are currently being used as flavorings (drinks, foods, confectionaries, perfumes, and cosmetics), sweeteners (drinks, foods, and confectionaries), colorants (drinks, foods, confectionaries, and cosmetics), antioxidants (drinks, foods, cosmetics, and health products), and other functional additives (health products, nutraceuticals, functional foods, beauty care products, and cosmeceuticals). These widespread trends in markets have resulted in a global demand for medicinal and aromatic plants of very high quality.

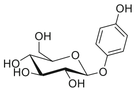
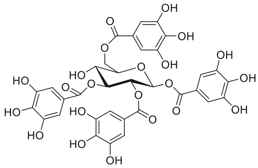
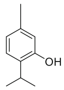
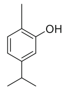
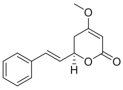
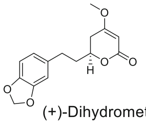
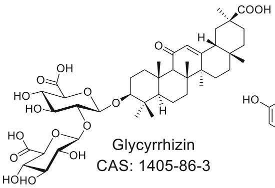
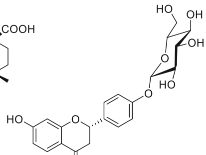
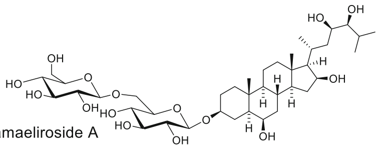
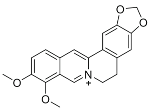
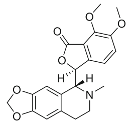
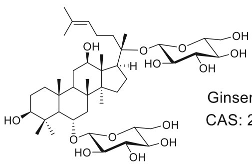
21.4 Non-sustainable Harvest of Plants

Raw materials from plants for use as herbal products such as herbal medicines, dietary supplements, food additives, and cosmetics are taken from both wild and cultivated plants. Worldwide, approximately two-thirds of all medicinal plants are harvested in the wild rather than from cultivated sources (Vines 2004).

About 15,000 species of medicinal plants are targeted in global concerns about depletion of wild populations, loss of habitat, invasive species, and pollution (Hamilton 2008). Non-sustainable harvesting of plants as sources of raw materials by commercial collectors has become a major cause of local extinctions and degradation of habitat.

There are well-documented examples of wild harvesting that have threatened populations of plant species and their habitats, which include *Arctostaphylos uva-ursi* (bearberry), *Thymus* spp. (wild thyme), *Piper methysticum* (kava kava), *Glycyrrhiza glabra* (liquorice), *Chamaelirium luteum* (false unicorn), *Hydrastis canadensis* (goldenseal), *Panax quinquefolius* (American ginseng), and *Panax ginseng* (Asian ginseng) (Vines 2004). Table 21.1 summarizes the chemical structures of the representative compounds in the popular herbal medicines listed above, along with the bioactivities reported as extracts or single substances, and major uses in industry (Abourashed and Khan 2001; Attele et al. 1999; Briskin 2000; Budzinski et al. 2000; Chan et al. 2000; Chen et al. 2017; Einbond et al. 2017; Gastpar and

Table 21.1 Phytochemicals of popular herbal medicines in the wild

Plant name	Chemical representative	Plant part	Activity	Use
Arctostaphylos uva-ursi (bearberry)	 Arbutin CAS: 497-76-7  1,2,3,6-Tetra-*O*-galloyl-β-D-glucose CAS: 79886-50-3	Leaf	Antiseptic Astringent Tyrosinase inhibitory	Urogential tract infections In cosmetic: skin-whitening
Thymus spp. (wild thyme)	 Thymol CAS: 89-83-8  Carvacrol CAS: 499-75-2	Leaf Stem	Antimicrobial Antifungal Antioxidant	Essential oil Postharvest diseases
Piper methysticum (kava kava)	 (+)-Kavain CAS: 500-64-1  (+)-Dihydromethysticin CAS: 19902-91-1	Root Rhizome	Antidepressant	Anxiolytic
Glycyrrhiza glabra (liquorice)	 Glycyrrhizin CAS: 1405-86-3  Liquiritin CAS: 551-15-5	Root Stolon	Antiinflammatory Estrogenicity	Expectorant Peptic ulcer
Chamaelirium luteum (false unicorn)	 Chamaeliroside A CAS: 1323952-20-0	Root Rhizome	Female reproductive health	
Hydrastis canadensis (goldenseal)	 Berberine CAS: 2086-83-1  (–)-Hydrastine CAS: 118-08-1	Root Rhizome	Antiinflammatory Antimicrobial Cytochrome P450 inhibitory	Tonic for appetite and digestion Inflammation Infection
Panax ginseng (Asian ginseng) *Panax quinquefolius* (American ginseng)	 Ginsenoside Rg_1 CAS: 22427-39-0	Root Rhizome	Antineoplastic Antistress Antioxidant	Cardiovascular CNS Endocrine Immune

Klimm 2003; Hamid et al. 2017; Li et al. 2016; Li et al. 2000; Martin et al. 2014; Van der Voort et al. 2003; Weber et al. 2003).

When medicinal plant species are threatened by wild harvesting, the damage can lead to a loss of genetic diversity and can increase the risk of adulteration from plants of the same genus, which can lead to a reduction, or loss, of the active components in the raw materials (Lubbe and Verpoorte 2011).

Generally, harvesting by local people for their own use is not a conservation problem. Industrial-scale harvesting of wild plants is harmful to sustainability (Hamilton 2008). The demand for medicinal plants as raw materials for use by industries is enormous and growing faster than the supply from the wild harvesting of slow-growing and limited plants in nature, which means over-harvesting by commercial collectors will continue until alternative methods of supply can be proposed.

21.5 Cultivation of Medicinal Plants

Cultivation is one solution to sustainable supply. Species with a large market share in the herbal medicines industry such as *Ginkgo biloba* (ginkgo), *Hypericum perforatum* (St. John's wort), and *Panax ginseng* (Asian ginseng) are now being cultivated by pharmaceutical and herbal companies, and some, such as Asian ginseng, have become rare in the wild (Canter et al. 2005; Vines 2004).

Cultivation has advantages as a method of supplying raw materials for commercial products. First, control of quality and quantity for raw materials is easier. The entirety of the supply chain from germination to harvesting is controlled with cultivated plants, which decreases the risks of adulteration and misidentification of plants. Under uniform conditions, cultivated plants generally have fewer chemical variations in terms of chemical profiles and content when only one variety is dealt with. Secondly, both the price and supply of raw materials tend to be stable. Wild harvests are more vulnerable to environmental problems such as invasive species, pollution, climate change, or trade regulations.

It is expensive to cultivate some plant species since investment and special technologies are needed for large-scale production. With medicinal and aromatic plants, however, the fear of losing a species as a wild resource of raw materials has provided great incentive to develop cultivation processes. For instance, many studies on the cultivation of *Glycyrrhiza* (liquorice) have been performed with Japanese herbal companies and academia to provide a stable supply because 100% of raw materials derived from liquorice in Japanese herbal medicines are imported from producer countries, and almost all of it comes from Chinese wild resources (JKMMA 2016; Akiyama et al. 2017).

One problem is that some herbal medicines are difficult to cultivate using normal processes. Cultivators often encounter phenomena such as low germination rates, slow growth rates, fast flowering, or low content of active compounds. In general, species with relatively small or local habitats must be cultivated with special treatment and/or under special environmental conditions that reproduce an environment similar to their natural habitat.

Environmental conditions for cultivation should be optimized based on the natural habitat because this greatly affects the growth of plants, the biosynthesis of secondary metabolite, and the accumulation of bioactive substances. To overcome low yields and low quality of cultivated plants, the use of some technologies has proven efficient and less labor-intensive.

Hydroponic growth of medicinal plants with underground parts (root, rhizome, stolon) that are used as raw materials has been established and applied to *Glycyrrhiza uralensis* (liquorice), *Atropa belladonna* (belladonna), and *Coptis japonica* (goldthread or canker root) in PFAL for 6 months to 1 year, which has successfully shortened the cultivation times for these slow-growing plants by almost 4 years, as well as promoting sufficient concentrations of active compounds (Yoshimatsu 2012). It generally takes 3 to 5 years of field cultivation or wild growth for the accumulation of targeted active compounds to reach the same levels of concentrations as those reaped by hydroponics cultivation.

21.6 Phytochemistry with Plant Factories

Recently, the high potential that PFALs possess for the cultivation of medicinal and aromatic plants has attracted the herbal product industry. The technology of PFAL can control environmental factors and provide comprehensive conditions in which medicinal plants can be cultivated on a commercial scale, even for plants that have special environmental requirements.

The goals of PFAL are to increase biomass yields along with uniformity in the concentration of phytochemicals based on standards of safety, quality, and efficacy. The chemical components in raw materials depend on the type of herbal products. For herbal medicines, increasing the concentration of bioactive compounds in extracts is important, and reducing the level of toxic ingredients, such as harmful compounds or heavy metals, is also essential. For food additives and cosmetics, beneficial compounds that are used as flavorings, sweeteners, colorants, and other functional additives are selected for increased production.

Again, plants have many hundreds of compounds, and it is very difficult to evaluate the potency of each. Therefore, processes of extraction and separation/purification for target compounds from cultivated plants are almost a necessity in order to standardize the safety, quality, and efficacy of raw materials. Uniformity in the concentrations of compounds in extracts can simplify the processes and make them more predictable while reducing the cost of raw materials. In industry, the desired compounds for specific products are generally the secondary metabolites produced in the plants. Difficulties in the cultivation of medicinal and aromatic plants are not confined to the enhancement of their growth but also include the regulation of secondary metabolites.

Plants produce targeted secondary metabolites through different biosynthetic pathways and accumulate them in different plant parts (roots, stems, leaves). The metabolic pathways by which target compounds are biosynthesized have been well investigated for some plants, and this has shown that secondary metabolites are adaptations to environmental stimuli such as fluctuating temperature and light conditions (antioxidants), stress (proline), infection (flavonoids), or herbivory (alkaloids) (Canter et al. 2005).

Environmental factors (temperature, humidity, light, water supply, minerals, and carbon dioxide) that can be controlled in PFAL influence plant metabolism. In addition, it is important to note that the accumulation of secondary metabolites is independently affected by various environmental conditions such as ultraviolet irradiation, drought, nutrient deficiency, and salinity as a response to abiotic stresses. In other words, secondary metabolites may be controlled intentionally with the addition of abiotic treatments. Therefore, the technology of a plant factory has great potential for easier regulation of secondary metabolites in the concentration of target compounds and for commercial production of raw materials with uniform quality.

An example of engineering changes in the concentrations of medicinal compounds was reported for *Perilla frutescens* grown in PFAL via the application of different environmental conditions (Lu et al. 2017). In that study, the concentration of rosmarinic acid (anti-allergic activity) was affected by light intensity and nutrient concentration in a hydroponic solution, and the highest concentration of rosmarinic acid was achieved with an optimized combination of light intensity and nutrient solution. The elicitor for accumulation of rosmarinic acid was the gap between the highest light intensity and the lowest nutrient solution, which resulted in low nutrient uptake stress to the perilla plant. Interestingly, the concentration of perillaldehyde (antimicrobial) that was produced through the monoterpene biosynthetic pathway was less affected by those stimuli than that of rosmarinic acid synthesized via the phenylpropanoid pathway.

This means that expression of phytochemicals in medicinal plants can be controlled by the fine regulation of every environmental condition and that the efficient production of targeted secondary metabolites can be enhanced in plants cultivated via PFAL technology.

21.7 Chemical Analysis of Medicinal Plants

21.7.1 Introduction

Chemical analysis of phytochemicals produced in medicinal and aromatic plants is conducted to evaluate their potency or function. Each bioactive compound that is responsible for the medicinal effect of an herbal medicine is primarily identified as the active principle compound. Since the potency of herbal medicines relies on the amount of the active compound, its concentration in raw materials must be determined via quantitative analysis. The compounds that add to the desired functions of herbal products are characterized as the main ingredients. Since the value of raw materials as functional additives is measured according to the main ingredients, the quality of raw materials is frequently assessed via their level of contamination.

21.7.2 Organic Molecules

Chemical analysis of secondary metabolites involves processes for extraction, separation, and identification. Every process involving organic molecules has been technologically developed and optimized for the successful analysis of secondary metabolites. With organic molecules, a method for each process is carefully selected by the characteristics and behavior of a target compound for analysis so that a suitable scheme can incorporate both speed and accuracy.

21.7.3 Extraction

Compounds are largely differentiated by their level of solubility in either water or organic solvents. Each secondary metabolite has a unique solubility. For instance, essential oils used as flavoring are mixtures of volatile and hydrophobic compounds produced in plants that are generally not soluble in water.

The aim of extraction is to use a solvent to extract compounds from solid materials and to concentrate the compounds in a solution for a separation process. The choice of a solvent that will dissolve a compound is most important. Nonpolar organic solvents, such as n-hexane, n-pentane, isopentane, and diethyl ether, are the preference for the extraction of nonpolar and volatile compounds, monoterpenoids (C10 unit) and phenylpropanoids, which are the secondary metabolites in essential oils. Hydrophilic compounds of secondary metabolites show low levels of volatility and are extracted using any mixture of polar and water-soluble solvents such as alcohols (e.g., methanol, ethanol), acetonitrile, acetone, and water.

Supercritical fluid extraction (SFE) is a method that is used to extract compounds via a supercritical fluid that is neither a gas nor a liquid. Supercritical fluids have physical properties (density, viscosity, diffusivity) that lie between those of gases and liquids; thus, the solubility of compounds in supercritical fluids can be more enhanced by the properties of supercritical fluids than by solvents. Carbon dioxide is typically used as a substrate of a supercritical fluid. Carbon dioxide is a nonpolar molecule in the chemical structure in a fluid and is suitable for the extraction of relatively nonpolar oils and fats; however, various applications that include nonvolatile triterpenoids (C30 unit) have proven that secondary metabolites can be extracted more efficiently and quicker by SFE either with the use of cosolvents or with the pretreatment of plant materials. SFE is now being utilized in the production of decaffeinated coffee and tea by the selective extraction/removal of caffeine from normal coffee beans and tea leaves.

21.7.4 Separation

Plants contain many hundreds of compounds as secondary metabolites. Extracts from the plants still contain hundreds of compounds even after screening by solubility via extraction. Some methods used to remove contamination from extracts are useful when the contamination may disturb the measurement of target compounds. In addition, those methods enhance the measurement sensitivity of target compounds by promoting detectable concentration levels. These methods include liquid-liquid extraction (also known as solvent extraction), solid phase extraction (SPE), and coagulation with filtration. Such pretreatment of extracts is time-consuming, but it is sometimes required in the preparation of samples intended for mass spectrometry.

21.7.5 Identification

21.7.5.1 Gas Chromatography: GC

Chemical analysis that uses a gas chromatograph is referred to as gas chromatography. The abbreviation "GC" frequently refers to both the process of gas chromatography and a gas chromatograph (JSAC 2011). Gas chromatography is the most dominant method used for the analysis of essential oils extracted from plants because it is specialized for the separation and identification of compounds that can be easily vaporized at temperatures from 250–350 °C. An essential oil extracted from medicinal and aromatic plants contains hundreds of monoterpenes and phenylpropanoids that are semi-volatile with relatively low boiling points.

A gas chromatograph equipped with either a flame ionization detector (FID) or a mass spectrometer is useful for the quantitative analysis of the compounds contained in essential oils. Gas chromatography/mass spectrometry (GC/MS) provides information about the chemical structures of the compounds detected by MS.

Electron impact (EI) is applied to GC/MS as an ionization method since it can effectively ionize gas-phase molecules via bombardment with a high-energy electron beam (Silverstein et al. 2005). The ions generated are recorded as the mass spectrum of ions that separate on the basis of mass/charge (*m/z*). The gas-phase method is applicable to compounds that vaporize under the operating temperature of a GC and are stable at that temperature. Those compounds typically have a molecular weight < 300. Monoterpenes (C10 unit) frequently show peaks of *m/z* 79, 93, 107, and 121 as fragment ions on the mass spectra (JSAC 2011).

Each of the compounds isolated by GC/MS shows a mass spectrum that is unique sufficiently for identification of the compounds by computer search that compares the similarities between the mass spectrum of the detected compound and that of known compounds in libraries and databases that currently register the EI mass spectra of more than 200,000 organic compounds from the results of GC/MS. This utility together with the great sensitivity of the EI method makes GC/MS a powerful and popular tool for chemical analysis.

21.7.5.2 High-Performance Liquid Chromatography: HPLC

High-performance liquid chromatography (HPLC) is applicable to many compounds that are not suitable for GC analysis. HPLC can be used to analyze the measurement of almost all secondary metabolites, including polyphenols with oxygen in the chemical structure. In contrast to GC, HPLC is widely used for less volatile compounds, because of their polar characteristics. A solution of extracts from plants in aqueous solvents is acceptable as a sample for HPLC, which has advantages that include simple preparation and easy handling of samples.

It is important to couple a liquid chromatograph to suitable detectors, such as ultraviolet-visible (UV-VIS) and MS. UV-VIS detectors include photodiode array (PDA) detectors, which are applicable to compounds that absorb UV and VIS light at wavelengths from 190 to 830 nm. Double-bonded carbon-carbon (C=C) and carbon-heteroatom (C=O, C=N, C=S) groups are frequently observed in the chemical structures of secondary metabolites, and they can produce UV-VIS absorbance characteristics on molecules. The UV-VIS absorbance spectrum recorded by PDA is useful in determining purity and in ensuring the isolation of a compound in a single peak that has been separated via HPLC, because the spectrum reflects all structures that have UV-VIS absorbance and can determine if the single peak represents a compound that is a single substance, a compound with contamination, or a mixture of compounds.

Liquid chromatography/mass spectrometry (LC-MS) has advanced rapidly with the development of electrospray ionization (ESI) around 1990. ESI uses polar and volatile solvents to ionize compounds in solution. The ionization method for the liquid-phase sample is applicable to compounds that are polar and hydrophilic and that have a molecular weight up to approximately 100,000. In addition, fragmentation of ions rarely occurs with ESI so that peaks related to molecular ions will appear on the mass spectrum characterizing the molecular weight of the detected compound. These features of ESI-MS make it a good match for LC and samples for LC analysis, which includes plant extracts.

21.8 Reference Standard of Herbal Medicine

The demand for reference standards is growing. Every chemical analysis needs a reference standard for compounds that must be identified. Quantitative analysis in particular requires a high-quality reference standard in order to determine the content of target compounds in medicinal and aromatic plants. Chemicals with great purity (>98%), accurate chemical formulas (molecular weight, hydration), and less contamination can be used in chemical analysis as reference standards. With the bioactive compounds that are used in pharmaceuticals and herbal medicines, moreover, there is less of a difference between the production of many batches, and traceability and a stable supply are requirements for reference standards with reliable quality.

Reference standards for herbal medicines are produced either by chemical synthesis or plant extraction. With production by chemical synthesis, achieving the requirements for a reference standard is feasible, but the results are not always an improvement over plant extraction because bioactive compounds in herbal medicines sometimes have an original element to their chemical structures (chirality, enantiomer, diastereomer) and chemical compositions (ingredients in essential oils).

Since a great many herbal products have become popular, the assurance of raw plant materials for use as reference standards is a concern for human health. To reproduce the natural essence of plants and conserve original plants, cultivation remains one of the best solutions, and the technology used in PFALs can insure both quality management and a stable supply via plant cultivation.

21.9 Conclusions

Medicinal and aromatic plants are valuable as sources of natural products that contribute to human health. The extract of a plant is a rich mixture of bioactive compounds that are responsible for both positive and negative effects on mental and physical conditions or symptoms. Advances in modern chemistry and biology have revealed the structure/activity relationships of bioactive compounds, and many clinical trials have validated the safety of their therapeutic effects on brains and bodies. It is commonly understood that the desired potency of plant extracts relies on the concentrations of the active natural compounds they contain. Herbal medicines and some food additives are derived from medicinal and aromatic plants, and to prove their safety and efficacy, chemical analyses of the concentrations of active natural compounds in raw plant materials are essential. The demand for high-quality medicinal and aromatic plants that are stable and of uniform quality is increasing in industries such as pharmaceutical, food, and cosmetics that consume these plants on an ever-increasing scale of commercial production.

With conservation of the sources of plant species, cultivation of medicinal and aromatic plants is attracting global attention from these industries as well as from academia, governments, and international unions. Generally, medicinal and aromatic plants should be cultivated with special environmental requirements serving as standards for the concentrations of desired compounds since the biosynthesis and accumulation of these compounds, mostly secondary metabolites, will be greatly affected by their growth environment.

PFALs can use technology to control every environmental factor and determine the optimized environment that will best enhance the production of targeted compounds by using a plant's metabolism. The practical merits of PFALs include increased biomass yields and uniformity in the concentrations of target compounds. PFALs can provide sustainable harvesting of medicinal and aromatic plants, which will conserve valuable source-plant species for future generations.

References

Abourashed EA, Khan IA (2001) High-performance liquid chromatography determination of hydrastine and berberine in dietary supplements containing goldenseal. J Pharm Sci 90 (7):817–822

Akiyama H, Nose M, Ohtsuki N et al (2017) Evaluation of the safety and efficacy of *Glycyrrhiza uralensis* root extracts produced using artificial hydroponic and artificial hydroponic-field hybrid cultivation systems. J Nat Med 71:265–271

Attele AS, Wu JA, Yuan CS (1999) Ginseng pharmacology: multiple constituents and multiple actions. Biochem Pharmacol 58:1685–1693

Briskin DP (2000) Medicinal plants and phytomedicines. Linking plant biochemistry and physiology to human health. Plant Physiol 124:507–514

Budzinski JW, Foster BC, Vandenhoek S et al (2000) An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 7 (4):273–282

Canter PH, Thomas H, Ernst E (2005) Bringing medicinal plants into cultivation: opportunities and challenges for biotechnology. Trends Biotechnol 23(4):180–185

Chan TWD, But PPH, Cheng SW et al (2000) Differentiation and authentication of *Panax ginseng*, *Panax quinquefolius*, and ginseng products by using HPLC/MS. Anal Chem 72(6):1281–1287

Chen YJ, Zhao ZZ, Chen HB et al (2017) Determination of ginsenosides in Asian and American ginsengs by liquid chromatography-quadrupole/time-of-flight MS: assessing variations based on morphological characteristics. J Ginseng Res 41:10–22

Einbond LS, Negrin A, Kulakowski DM et al (2017) Traditional preparations of kava (*Piper methysticum*) inhibit the growth of human colon cancer cells in vitro. Phytomedicine 24:1–13

Gastpar M, Klimm HD (2003) Treatment of anxiety, tension and restlessness states with Kava special extract WS® 1490 in general practice: a randomized placebo-controlled double-blind multicenter trial. Phytomedicine 10:631–639

Hamid HA, Ramli ANM, Yusoff MM (2017) Indole alkaloids from plants as potential leads for antidepressant drugs: a mini review. Front Pharmacol 8:96

Hamilton AC (2008) Medicinal plants in conservation and development: case studies and lessons learnt, 4 pp, Plantlife International. www.plantlife.org.uk

Houghton PJ (2001) Old yet new-pharmaceuticals from plants. J Chem Educ 78(2):175–184

Japan Kampo Medicines Manufacturers Association [JKMMA] (2016) Report on investigation of usage of the crude drugs for Kampo preparation (4) – the usage in FY2013 and FY2014. 3–11 pp. www.nikkankyo.org/aboutus/investigation/pdf/shiyouryou-chousa04.pdf

Japan Society for Analytical Chemistry [JSAC] (2011) Shokuhin-bunseki. Maruzen Publishing Co. Ltd., Tokyo, 47–63 pp (in Japanese)

Japanese Pharmacopeia, 17th Edn. [JP17] (2016) General notices: 1 pp. official monographs, crude drugs and related drugs: 1791–2012 pp. http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000066597.html

Li WK, Gu CG, Zhang HJ et al (2000) Use of high performance liquid chromatography-tandem mass spectrometry to distinguish *Panax ginseng* C. A. Meyer (Asian ginseng) and *Panax quinquefolius* L. (North American ginseng). Anal Chem 72(21):5417–5422

Li GN, Nikolic D, van Breemen RB (2016) Identification and chemical standardization of licorice raw materials and dietary supplements using UHPLC-MS/MS. J Agric Food Chem 64 (42):8062–8070

Lu N, Bernardo EL, Tippayadarapanich C et al (2017) Growth and accumulation of secondary metabolites in perilla as affected by photosynthetic photon flux density and electrical conductivity of the nutrient solution. Front Plant Sci 8:708

Lubbe A, Verpoorte R (2011) Cultivation of medicinal and aromatic plants for specialty industrial materials. Ind Crop Prod 34(1):785–801

Martin AC, Johnston E, Xing CG et al (2014) Measuring the chemical and cytotoxic variability of commercially available kava (*Piper methysticum* G. Forster). PLoS One 9(11):7

Silverstein RM, Webster FX, Kiemle DJ (2005) Spectrometric identification of organic compounds, 7th edn. Wiley, Hoboken, 1–8 pp

Van der Voort ME, Bailey B, Samuel DE et al (2003) Recovery of populations of goldenseal (*Hydrastis canadensis* L.) and American ginseng (*Panax quinquefolius* L.) following harvest. Am Midl Nat 149(2):282–292

Vines G (2004) Herbal harvests with a future: towards sustainable sources for medicinal plants. Plantlife International. www.plantlife.org.uk

Weber HA, Zart MK, Hodges AE et al (2003) Chemical comparison of goldenseal (*Hydrastis canadensis* L.) root powder from three commercial suppliers. J Agric Food Chem 51 (25):7352–7358

Yoshimatsu K (2012) Innovative cultivation: hydroponics of medicinal plants in the closed-type cultivation facilities. J Trad Med 29(1):30–34