Wild Plants, Mushrooms and Nuts

Wild Plants, Mushrooms and Nuts: Functional Food Properties and Applications

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Preface

The use of healthy ingredients is a natural way of preventing diseases and contributes to the increased use of natural matrices. This book focuses on the nutritional, chemical, and biological properties of natural matrices from the Iberian peninsula, mainly food products such as wild plants, mushrooms, chestnuts, and almond.

Society's attitude to food, as a natural and inevitable necessity, has altered in line with changes in social conditions and development of technology. Current consumers are interested in the composition, properties, safety, and health effects of food products. The desire to consume foods with high biological value from natural origins poses a huge challenge for modern food science and industry. In addition, the recent consumer interest in chemopreventive nutrition has increased the choice of food products (functional foods) with specific components (bioactive compounds). The current increase in the adoption of more active and healthy lifestyles needs to be followed by a concomitant response from all players in the food chain. The knowledge contained in this book will allow scientists and, in the longer term, lay members of society to gain a better understanding of the value that these products exhibit, focusing on their nutritional and chemical composition, bioactivity, and potential as functional foods.

Ongoing research on selected products will lead to a new generation of foods, and will promote their nutritional and medicinal use. Public health authorities consider prevention and treatment with nutraceuticals a powerful instrument in maintaining and promoting health, longevity, and life quality. The beneficial effects of nutraceuticals will undoubtedly have an impact on nutritional therapy; they also represent a growing segment of today's food industry. Therefore wild plants, mushrooms, and nuts have become interesting food products due to the increasing interest in the concept of "functional foods" with "health benefits."

Wild Plants, Mushrooms and Nuts: Functional Food Properties and Applications is a compendium of current and novel research on the chemistry, biochemistry, nutritional and pharmaceutical value of traditional food products, which are becoming more relevant in our current diet, for developing novel health foods and in modern natural food therapies. Topics covered range from their nutritional value, chemical and biochemical characterization, to their multifunctional applications as food with beneficial effects on health, through their biological and pharmacological properties (antioxidant, antibacterial, antifungal, and antitumor capacity, among others).

9

Wild Plant-Based Functional Foods, Drugs, and Nutraceuticals

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9.1 Introduction

Wild plants were originally the main element in the human diet, culminating in the different cultures and societies of today. However, the establishment of agriculture led to the decline of consumption of wild plants in comparison to the cultivars that could be grown every year (Grivetti & Ogle 2000). Nevertheless, consumption of wild plants is still a tradition that remains in many cultures, either for their nutritional and health benefits or for sociocultural behaviors that characterize many societies (Groot *et al*. 2002; Pardo de Santayana *et al*. 2007; Schulp *et al*. 2014). As human health and nutrition are two of the pillars that sustain our survival, it is necessary to find new ways to support medical care, which can be found in the vast wild plant ecosystem (Heywood 2011).

Food with additional functional properties could be the future of health supplies for the world population, and thus food and drugs are increasingly seen as one matrix (Bernal *et al*. 2011). Functional foods, nutraceuticals, and drugs based on wild plants that are still unexplored are emerging as a response to the world market, which has been searching for new, better, and safer products.

Functional foods have a similar appearance to their traditional counterparts, but bring potential beneficial effects when consumed on a regular basis in a varied diet. On the other hand, nutraceuticals are substances that have positive physiological effects on the human body, being consumed in unit dose forms such as tablets, capsules or liquids, allowing the delivery of a concentrated bioactive agent and providing a dose that could not be obtained from a normal food intake (Gulati & Ottaway 2006; Hasler 2000). Both the functional food and nutraceutical sectors have been growing significantly in Europe but in the European Union nutraceuticals are not

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considered as a specific food category with a series of rules and guidelines to define the product itself, obeying the general regulations on food safety, traceability, recall, and notification (Coppens *et al.* 2006; Gulati & Ottaway 2006). In terms of the health claims associated with functional foods, relating to Regulation (CE) No. 1924/2006 of the European Parliament on nutritional claims and health properties of food, it is possible to classify a functional food under very strict rules and conditions. In addition to the legislation required for all foodstuffs, scientific evidence of the health claims regarding the relevant food will be mandatory for all new products (Bech-Larsen & Scholderer 2007). In the United States, on the other hand, the Food and Drug Administration (FDA) defines the product's category depending on its characteristics, nutraceuticals being regulated as a food and beverage product and dietary supplement, covered by several safety issues, health claims, labeling, and good manufacturing practices (Milner 2000; Wrick 2005).

Concerning drug development, the market also requires safer products due to increasing worldwide concern about synthetic chemical compounds. In that respect, wild plant-based drugs are now in the forefront of the therapeutic agents used for human health, taking into account their high efficiency and low toxicity (Bhardwaj *et al.* 2014; Carocho & Ferreira 2013a).

In this chapter, wild plants commonly used as functional foods will be reviewed. For nutraceuticals, the emerging concept, their applications and novel formulations will be described, and also some products already available on the market. The relationship between the bioactive phytochemical and the active principle will be explained, listing the common formulations in wild plant-based drugs and the different therapeutic targets that can be explored.

9.2 Wild Plants and Functional Foods

9.2.1 The Concept and Recent Trends in Functional Foods

In the first half of the twentieth century, the focus of nutritional science was on establishing the minimum requirements for essential nutrients that ensure the avoidance of deficiency diseases (MMWR 1999). Nowadays, these concepts are changing significantly in the industrialized world. We are progressing from a concept of "adequate nutrition" to one of "optimal nutrition" (Ashwell 2003); from a matter of survival, satisfying hunger, and ensuring food safety to an emphasis on the potential for foods to promote health, in terms of both preventing nutrition-related diseases and improving physical and mental wellbeing (Nöthlings *et al.* 2007; Takachi *et al.* 2008). In addition, consumers are increasingly better informed about the subject than they were in the past. As a result, their expectations of obtaining health benefits from the food they eat are also increasing (Diplock *et al.* 1999). These changes can be explained by some significant trends in our present society, namely rapid advances in science and technology, the rising costs of healthcare, the increase in the numbers of elderly people and in average life expectancy, changes in food laws affecting label and product claims, and people's desire for a better quality of life (Roberfroid 2007).

The primary role of food is to provide nutrients to meet human metabolic requirements and to give the consumer a feeling of satisfaction and wellbeing through hedonistic attributes such as taste. In addition to this, food can fulfill specific physiological functions in the human body (Li *et al.* 2014a; Zhang *et al.* 2015). In fact, food can not only help to achieve optimal health and development, but it might also play an important role in reducing or preventing the risk of disease. According to the World Health Organization (WHO) and Food and Agriculture Organization (FAO), several dietary patterns along with lifestyle habits constitute major modifiable risk factors in relation to the development of coronary heart disease, different types of cancer, diabetes, obesity, osteoporosis, and periodontal disease (WHO 2003). Foods with these properties were first regulated in Japan in 1981 as Foods for Specified Health Use (FOSHU) (Hasler 2002; Ohama *et al.* 2006). Later, in Europe, the project Functional Food Science in Europe (FUFOSE) was created to assess critically the science base required to provide evidence that specific nutrients and food components beneficially affect target functions in the human body (Tijhuis *et al.* 2012). Currently, this kind of food is generally referred to as "functional food," if in accordance with the definition given below.

Although there is no universally accepted definition for functional foods (Hasler 2002), and because functional foods are more of a concept than a well-defined group of food products, here we present the definition described previously by Diplock *et al.* (1999). According to these authors, a food can be regarded as "functional" if it is satisfactorily demonstrated to affect beneficially one or more target functions in the human body, beyond adequate nutritional effects, in a way relevant to either an improved state of health and wellbeing and/or disease risk reduction. These foods must remain foods in appearance and they must demonstrate their effects in amounts that can normally be expected to be consumed in the usual diet, i.e. they are not pills or capsules, but part of a normal food pattern. Additionally, a functional food can be a natural or unmodified food, or one to which a component has been added or removed by technological or biotechnological means. It can also be a food where the nature of one or more components has been modified, the bioavailability altered, or any combination of these possibilities. Additionally, a functional food might be functional for all members of a population or for particular groups only. It is also important to note that, along with the nonuniversal definition, global markets also do not have the same regulatory systems for these foods (Bagchi 2014).

Functional food science is still at an early stage in its development. However, since knowledge about the functional effects of foods is increasing and the functionality of particular foods and food components is more extensively recognized, technology will have a continuing role to play in making those foods and food components more widely available and accessible (Howlett 2008). On the other hand, it is now known that genetic factors influence the relationship between diet and disease, and the ways in which different protective and risk factors can act. Furthermore, it is possible to visualize differences between genetic profiles of individuals at the molecular level and understand how they relate to differences between those individuals' responses to physiological factors. Thus, in the near future, knowledge gained in the fields of genomics, proteomics, and metabolomics (collectively known as "omics") will be of great importance for the development of functional foods and to create customized diet programs, as well as verifying the influence of dietary factors on human health and disease, which can lead to the identification of new food functionality routes (Howlett 2008).

9.2.2 Classification and Development of Functional Foods

Functional foods represent one of the most interesting and active areas of research and innovation in the food industry (Annunziata & Vecchio 2011). Their design and development, besides being an expensive process (Betoret *et al.* 2011), is a key issue, as well as a scientific challenge, which should rely on basic scientific knowledge relevant to target functions and their possible modulation by food components (Diplock *et al.* 1999). It is possible to separate them into natural (or nonaltered) and modified functional foods. But whether modified or not, they should always be safe, without any consideration of a trade-off between health benefit and health risk. More specifically, and according to the definition of functional foods presented before, they can be classified as:

- *nonaltered products*: foods naturally containing increased content of nutrients and/or health-promoting compounds
- *fortified products*: foods wherein the content of the existing components is increased
- *enriched products*: foods to which a component not normally found is added to provide benefits
- *altered products*: foods in which a component is removed or replaced by an alternative component with favorable properties
- *enhanced commodities*: the food composition is altered by changing the raw commodity, i.e. one of the components is enhanced through special growing conditions, breeding, or biotechnological means.

Although the functional food industry is growing steadily worldwide, the successful commercialization of new functional foods remains a challenge, especially due to the need for a strategic approach to their production processes (Howlett 2008). For this reason, during the development or reengineering of modified functional foods, it is necessary to take into account many variables, such as sensory acceptance, convenience, stability, chemical and functional properties, and price (Betoret *et al.* 2011; Granato *et al.* 2010). In fact, the relationship "structure-property" needs to be noted, once the functional effect depends on the active component gaining access to the functional target site. However, foods are mostly complex mixtures that can trap active compounds, modulate their release, or inhibit their activity. Thus, the food matrix in its raw state, after culinary preparation, or storage can have a significant influence on the activity or release of the key components. According to Betoret *et al.* (2011), the design of appropriate food vehicles to maintain the active form until the time of consumption, and to deliver this form to the desired target site within the organism, is vital to the success of functional foods.

Betoret *et al.* (2011) grouped the available technologies for functional foods development into three main categories. The first group is formed by the most commonly used technologies for functional foods development, including technologies traditionally used in food processing, formulation, and blending as well as for cultivation and breeding. The second group, constituted by methodologies that form a structure to try to prevent the deterioration of physiologically active compounds, includes microencapsulation, edible films and coatings, and vacuum impregnation technologies. The third group, formed by recent technologies that are intended to design functional foods aimed at personalized nutrition, is the one that has grown significantly in recent years.

9.2.3 Wild Plants Used as Functional Foods

Plants are irreplaceable food resources for humans. Their interchangeable use as foods and as medicines, or healthy foods, has been part of human heritage since prehistoric times. Despite only a small number of existing plant foods having substantial clinical documentation of their health benefits, an even smaller number (and including only cultivated plants) have surpassed the rigorous standard of "significant scientific agreement" required by the FDA and EFSA for authorization of a health claim (Hasler 2002). Oat soluble fiber, soluble fiber from psyllium seed husk, soy protein and sterol and stanol ester-fortified margarine are plant-based foods currently eligible to bear an FDA-approved health claim (Hasler 2002). However, there is growing clinical research supporting the potential health benefits of various plant foods (including wild plants) or food constituents that currently do not have approved health claims, and thus are described as having "moderately strong evidence." Examples include berries, leafy vegetables, garlic, grapes and chocolate, among others listed in Table 9.1.

Table 9.1 presents wild edible plants that have been investigated due to their claimed functional properties. These plants are interesting sources of physiologically active ingredients which are linked to various beneficial health effects. Various berries, including elderberry, bilberry, cranberry, blackberry, raspberry, and wild strawberry, stand out as a source of anthocyanins, proanthocyanidins, flavonols, phenolic acids, and vitamins, among other bioactive compounds. These molecules, isolated or in combined extracts, have antioxidant, antiinflammatory, anticarcinogenic, cardioprotective, and antibacterial properties (Barros *et al.* 2011a; Bowen-Forbes *et al.* 2010; Madhavi *et al.* 1998; Najda *et al.* 2014; Sidor & Gramza-Michalowska 2014; Singh *et al.* 2009). Wild strawberry fruits harvested from natural habitats were highlighted by Najda *et al.* (2014) as containing more anthocyanins and higher antioxidant activity than those from cultivation. Likewise, Lv *et al.* (2014) showed that the wild litchi cultivar Hemaoli has high total phenolic and flavonoid content in comparison to one of the main market cultivars. This fruit also has high levels of carotenoids and vitamin C, which contribute to its antioxidant, antiapoptotic, and hepatoprotective effects (Bhoopat *et al.* 2011; Huang *et al.* 2010a; Lv *et al.* 2014). Physalis (*Physalis* spp.) is another berry with claimed functional properties. Physalins, withanolides, sterols, polysaccharides, and flavones are compounds present in this golden berry. According to Li *et al.* (2014c), it has antiinflammatory, antioxidant, antitumor, hypoglycemic, and analgesic properties.

Other plants, like the root of beet (*Beta* spp.), have antioxidant, hepatoprotective, anticancer, and antiproliferative activity in MRC5 and MCF-7 cell lines, antihypertensive, and hypoglycemic effects. These health benefits are conferred by the high content of phenolic acids, flavonoids, betalains, minerals (P, Mg, Fe, Zn, Ca, and Na), folic acid, biotin, and soluble fiber (Ninfali & Angelino 2013; Vulić *et al.* 2014; Wootton-Beard & Ryan 2011). In turn, ginger (*Zingiber officinale* Rosoe) has been described as a source of gingerols (6-gingerol), shogaols (6-shogaol), fiber, and flavonoids, as well as having antioxidant, antiinflammatory, antithrombotic, cholesterol-lowering, analgesic, antipyretic, and hypotensive effects (Mojani *et al.* 2014; Thomson *et al.* 2002).

Regarding leafy vegetables, the aerial parts of water blinks (*Montia fontana* L.) have high amounts of tocopherols and vitamin C, compounds that provide antioxidant benefits (Morales *et al.* 2012; Pereira *et al.* 2011), while watercress (*Nasturtium officinale* W.T. Aiton) is a rich source of phenolic compounds and minerals (P, Mg, Ca, and Mn)

Table 9.1 Some wild edible plant foods claimed to have functional properties.

Plant species	Common name and used part	Evaluated extract	Functional compounds	Potential health benefits	Reference
Allium ampeloprasum L.	Wild leek (bulb)	Aqueous and ethanolic extracts	Fiber, zinc, polyunsaturated fatty acids (mainly palmitic acid), polysaccharides (glucofructan), and steroidal saponins	Antioxidant, antiinflammatory, antiulcerogenic, and gastroprotective	Adão *et al.* 2011; García-Herrera *et al.* 2014; Malafaia *et al.* 2015
Arbutus unedo L.	Strawberry tree (fruit)	Methanolic, hydromethanolic (80%), and phenolic extracts	Tocopherols, ascorbic acid, flavan-3-ols, and galloyl derivatives	Antioxidant activity and antitumor potential against NCI-H460 human cell line	Barros *et al.* 2010; Guimarães *et al.* 2013, 2014
Asparagus acutifolius L.	Wild asparagus (shoots)		Tocopherols, vitamin C, and glycosides of flavonols	Antioxidant	Barros *et al.* 2011b; Martins *et al.* 2011
Beta spp.	Beet (root)	Aqueous, hydroethanolic, methanolic, and betalain-rich extracts and juice	Phenolic acids (ferulic, vanillic, *p*-hydroxybenzoic, caffeic and protocatechuic acids), flavonoids (catechin, epicatechin, rutin and vitexin), betalains (betanin, isobetanin and vulgaxanthin I), minerals (potassium, magnesium, iron, zinc, calcium, sodium), folic acid, biotin and soluble fiber	Antioxidant, hepatoprotective, anticancer, antiproliferative activity in MRC5 and MCF-7 cell lines, antihypertensive and hypoglycemic	Wootton-Beard & Ryan 2011; Ninfali & Angelino 2013; Vulić *et al.* 2014
Capparis decidua (Forssk.) Edgew.	Caper or kair (fruit)	Aqueous, methanolic, acidified methanolic, hydroalcoholic, and ethanolic extracts	N-pentacosane, β-sitosterol, β-carotene, alkaloids, phenolic compounds including flavonoids and minerals (manganese, copper, and iron)	Antioxidant, antidiabetic, diuretic, hypercholesterolemic, antihypertensive, antiatherosclerotic, hypolipidemic, antimicrobial, and anthelmintic	Rathee *et al.* 2010 ; Sharma *et al.* 2010; Zia-Ul-Haq *et al.* 2011; Shad *et al.* 2014

Dimocarpus longan Lour.	Longan (fruit)	Aqueous, hydromethanolic (80%), acetone:ethanol (1:1, v/v), hydroacetone (70%) and polyphenol-rich extracts	Phenolic compounds (corilagin, gallic and ellagic acids, flavone glycosides, glycosides of quercetin and kaempferol and epicatechin), vitamin C, fiber, and minerals	Antioxidant, antiinflammatory, antityrosinase, antiglycated, anticancer, and memory-enhancing effects	Huang *et al.* 2010a; Yang *et al.* 2011; Huang *et al.* 2012
Eugenia uniflora L.	Pitanga or Brazilian cherry (fruit)	Ethyl acetate and ethanolic extracts	Anthocyanins, flavonols, and carotenoids	Antidiarrheic, diuretic, antirheumatic, antifebrile, antidiabetic, antimicrobial, and antitrypanosoma	Costa *et al.* 2013
Euterpe oleracea Mart.	Acai, assai or açaí (fruit)	Ethyl acetate, *n*-buthanolic, hydromethanolic (50%), and hydroacetonic (70%) extracts	Flavonoids (anthocyanins and procyanidin), phenolic acids, lignans, and stilbenes	Antioxidant, antiallergic, anticancer, antiinflammatory, atheroprotective, improves the endothelial function and platelet aggregation, vasodilation, and prevents cardiovascular disease	Rufino *et al.* 2010 ; Kang *et al.* 2011; Costa *et al.* 2013
Ficus carica L.	Fig (fruit)	Hexane, methanolic, and hydromethanolic extracts	Phenolic acids (chlorogenic acid), anthocyanins, flavonols, flavones (luteolin), minerals (iron, potassium, sodium and calcium), fiber, sugars, and vitamin A	Antioxidant, anticholinesterase, anticarcinogenic, antiproliferative activity in several cancer cell lines, digestive, antifungal, and anthelminthic	Huang *et al.* 2010a; Barolo *et al.* 2014; Shad *et al.* 2014
Fragaria vesca L.	Wild strawberry or European strawberry (fruit)	Aqueous extracts and combined extract of *n*-buthanolic and to HCl (1 mol/ dm^3)	Flavonoids (e.g. anthocyanins), phenolic acids, and salicylic acid	Antioxidant	Najda *et al.* 2014
Garcinia mangostana L.	Mangosteen or purple mangosteen (fruit)	Aqueous, methanolic, ethanolic, hydroethanolic (40 and 50%), and juice extracts	Xanthones (α-, β-, and γ-mangostins, garcinone E, 8-deoxygartanin and gartanin)	Antioxidant, antitumor, antiproliferative, proapoptotic, antiinflammatory, antiallergic, antibacterial, antifungal, antiviral, antimalarial, antidiabetic, antihiperlipidemic and antiatherogenic, cardioprotective, hepatoprotective, immunomodulator, and antiulcer	Pedraza-Chaverri *et al.* 2008; Gutierrez-Orozco & Failla 2013

(*Continued*)

Table 9.1 (Continued)

Plant species	Common name and used part	Evaluated extract	Functional compounds	Potential health benefits	Reference
Gardenia jasminoides J. Ellis	Gardenia (fruit)	Hydromethanolic (80%), hydroethanolic (60%), and cetone:ethanol (1:1, v/v) extracts	Caffeoylquinic acid derivatives (chlorogenic acid, dicaffeoylquinic acid and other caffeoyl-conjugate quinic acid derivatives), flavonoids (rutin), iridoids (geniposide), and carotenoids (crocin)	Antioxidant and antiinflammatory	Huang *et al*. 2010a; Peng *et al*. 2013
Litchi chinensis Sonn.	Litchi or lychee (fruit)	Methanolic (70% and 80%), acetone:ethanol, (1:1) and juice extracts	Phenolic compounds (cinnamic acid and procyanidins), carotenoids, and vitamin C	Antioxidant, antiapoptotic, and hepatoprotective	Huang *et al*. 2010a; Bhoopat *et al*. 2011; Lv *et al*. 2014
Lycium barbarum L.	Goji berry (fruit)	Aqueous, methanolic, and crude and purified polysaccharide extracts	Polysaccharides, carotenoids (zeaxanthin), betaine, cerebroside, β-sitosterol, *p*-coumaric acid, and vitamin C	Antioxidant, antiaging, antiinflammatory, anticancer, cytoprotective, neuroprotective, metabolism stimulator, glucose regulator in diabetics, glaucoma (eye health benefits), immunomodulatory, antibacterial and cardioprotective	Amagase & Farnsworth 2011
Malpighia emarginata D.C.	Acerola or wild crepe myrtle (fruit)	Methanolic, hydromethanolic (50%), hydroacetonic (70%), and aqueous extracts and juice	Vitamin C, carotenoids (β-carotene), riboflavin, thiamine, fiber, minerals (phosphorus, calcium, and iron), anthocyanins (cyanidin-3-rhamnoside and pelargonidin-3-rhamnoside) and flavonols (quercetrin)	Antioxidant, antiaging, antiinflammatory and prevents weight gain and dyslipidemia	Mezadri *et al*. 2008; Rufino *et al*. 2010 ; Delva & Goodrich-Schneider 2013; Dias *et al*. 2014
Montia fontana L.	Water blinks (aerial parts)	Methanolic extract	Tocopherols and vitamin C	Antioxidant	Pereira *et al*. 2011; Morales *et al*. 2012

Myrciaria cauliflora (Mart.) O. Berg	Jaboticaba or guapuru (fruit)	Methanol:formic acid (9:1, v/v), methanol:water:acetic acid (85:15:0.5, v/v/v/), methanolic, hydromethanolic (50%), ethanolic, acetonic, and hydroacetonic (70%) extracts	Anthocyanins, ellagic and gallic acid, carotenoids, depsides, tannins, rutin, and vitamin C	Antioxidant, antiinflammatory, inhibits IL-8 production, antiproliferative effects against tumor cells, protective effect in cardiovascular disease and type 2 diabetes mellitus	Rufino *et al.* 2010; Leite *et al.* 2011; Costa *et al.* 2013
Myrciaria dubia (Kunth.) McVaugh	Camu-camu, cacari or camocamo (fruit)	Hydromethanolic (50%) and hydroacetonic (70%) extracts	Anthocyanins, myricetin and conjugates, ellagic acid and conjugates, ellagitannins, flavan-3-ols, proanthocyanidins, and vitamin C	Antioxidant, antiinflammatory and inhibits the LPS-induced NO release in RAW 264.7 cells	Rufino *et al.* 2010 ; Costa *et al.* 2013; Fracassetti *et al.* 2013
Nasturtium officinale W. T. Aiton	Watercress (aerial parts)	Methanolic and hydromethanolic (70%) extracts	Phenolic compounds and minerals (phosphorus, potassium, calcium, and manganese)	Antioxidant, anticarcinogenic, and chemopreventive	Pereira *et al.* 2011; Manchali *et al.* 2012
Origanum vulgare L.	Oregano (aerial parts)	Aqueous (infusions and decoctions) and hydromethanolic extracts (80%)	Flavonoids and phenolic acids	Antioxidant and antimicrobial potential	Martins *et al.* 2014
Physalis spp.	Physalis or golden berry (fruit)	Hydroethanolic (70%) extracts	Physalins, withanolides, sterols, polysaccharides, and flavones	Antiinflammatory, antioxidant, antitumor, hypoglycemic, and analgesic	Li *et al.* 2014c
Prosopis cineraria (L.) Druce	Ghaf, khejri, sami or golden tree of Indian deserts (pod)	Aqueous and methanolic extracts	Triterpenoids (3-benzyl-2-hydroxy-urs-12-en-28-oic acid and maslinic acid-3 glucoside), fatty acid (linoleic acid), piperidine alkaloid (prosophylline) and polyphenols (5,5′-oxybis-1,3-benzenediol, 3,4,5-trihydroxycinnamic acid 2-hydroxyethyl ester and 5,3′,4′-trihydroxyflavanone 7-glycoside)	Antioxidant and antiinflammatory	Liu *et al.* 2012

(*Continued*)

Table 9.1 (Continued)

Plant species	Common name and used part	Evaluated extract	Functional compounds	Potential health benefits	Reference
Prunus spinosa L.	Blackthorn or sloe (fruit)	Methanolic and phenolic enriched extracts	Ascorbic acid, phenolic acids and flavonoids (anthocyanins, flavonols and flavones)	Antioxidant and antitumor potential	Barros *et al.* 2010; Guimarães *et al.* 2013, 2014
Psidium cattleianum Sabine	Strawberry guava (fruit)	Hexane, ethyl acetate, acetonic, aqueous, ethanolic, and methanolic extracts	Phenolic compounds (ellagic acid, ellagic acid deoxyhexoside and epicatechin gallate), carotenoids, vitamin C, and fiber	Antioxidant, antiinflammatory, and antimicrobial	McCook-Russell *et al.* 2012; Ribeiro *et al.* 2014
Psidium guajava L.	Guava (fruit)	Methanolic, hydromethanolic (80%), acetone:ethanol (1:1, v/v), hexane, ethyl acetate and ethanol/water/formic acid (70:25:5, v/v/v) extracts	Phenolic acids (chlorogenic acid), flavan-3-ols (catechin), anthocyanins (delphinidin-3-*O*-glucoside and cyanidin-3-*O*-glucoside)	Antioxidant, antiinflammatory, and antimicrobial	Huang *et al.* 2010a; McCook-Russell *et al.* 2012; Flores *et al.* 2015
Punica granatum L.	Pomegranate (fruit)	Aqueous, ethyl acetate, acetonic, and methanolic extracts	Anthocyanins, gallotannins, ellagitannins (ellagic acid, gallic acid, and punicalagin), gallagyl esters, hydroxybenzoic and hydroxycinnamic acids and dihydroflavonol	Antioxidant, antiinflammatory, antiallergic, chemopreventive, anticancer, cardioprotective, gastroprotective, antimicrobial, and anthelminthic	Ismail *et al.* 2012
Rhodomyrtus tomentosa (Aiton) Hassk.	Rose myrtle (fruit)	Hexane, methanolic, hydromethanolic (80%), acetone:ethanol (1:1, v/v), acetone:water:acetic acid (50:49:1, v/v/v), and flavonoid-rich extracts	Flavonoids (gallocatechin gallate, dihydromyricetin, quercetin, kaempferol, anthocyanins and vitexin), organic acids, polysaccharides, fiber, vitamin E (α-tocopherol), minerals (manganese and copper) and essential fatty acids (mainly linoleic acid)	Antioxidant	Huang *et al.* 2010a; Lai *et al.* 2015; Wu *et al.* 2015

Rubus spp.	Blackberry and raspberry (fruits)	Hexane, ethyl acetate, and methanolic extracts	Anthocyanins, flavonols, phenolic acids (ellagic acid), vitamins C and E, folic acid, and β-sitosterol	Antioxidant, antiinflammatory, and chemopreventive	Bowen-Forbes *et al*. 2010
Sambucus nigra L.	Elderberry, black elder or European elder (fruit)	Methanolic, acidified methanolic, ethanolic, and hydroethanolic (80%) extracts	Polyphenols (anthocyanins, flavonols, phenolic acids and proanthocyanidins), terpenes, lectins, unsaturated fatty acids, fiber, vitamins A, B, C and E, and minerals	Antioxidant, cardiovascular protection, antidiabetic and antiobesity, reinforces the immune system, antiviral, antibacterial, and UV radiation protector	Barros *et al*. 2011a; Sidor & Gramza-Michałowska 2014
Syzygium cumini (L.) Skeels.	Jambul or jambolan (fruit)	Methanolic, hydromethanolic (50%), hydroacetonic (70%), and hexane extracts	Anthocyanins, phenolic acids (ellagic acid), flavonols (quercetin and rutin), carotenoids, vitamin C, and manganese	Antioxidant, antiscorbutic, diuretic, and antidiabetic	Rufino *et al*. 2010; Costa *et al*. 2013; Shad *et al*. 2014
Vaccinium myrtillus L.	Bilberry (fruit)	Acidified methanolic, ethyl acetate, hexane, anthocyanins, and proanthocyanidin-rich extracts	Flavonoids (proanthocyanidins and anthocyanins), carotenoids (lutein and zeaxanthin), and sterols	Antioxidant, antibacterial (inhibition of urinary tract infections), anticarcinogenic and antiproliferative activity in two human breast cancer cell lines MCF-7 and BT-20	Madhavi *et al*. 1998
Vaccinium spp.	Cranberry (fruit)	Hydroacetonic (80%), ethyl acetate, and phenolic extracts	Phenolic acids and flavonoids (anthocyanins, proanthocyanidins, and flavonols)	Antioxidant, antiinflammatory and cardiovascular and urinary tract protection	Singh *et al*. 2009; Khoo & Falk 2014
Zingiber officinale Rosoe	Ginger (rhizome)	Aqueous and methanolic extracts	Gingerols (6-gingerol), shogaols (6-shogaol), fiber, and flavonoids	Antioxidant, antiinflammatory, antithrombotic and cholesterol lowering, analgesic, antipyretic, and hypotensive	Thomson *et al*. 2002; Mojani *et al*. 2014
Ziziphus jujuba Mill.	Jujube or red date (fruit)	Aqueous, hexane, methanolic, and hydromethanolic extracts	Saponins, tannins, terpenoids, flavonoids, and iron	Antioxidant, antiinflammatory, and gastrointestinal protector	Yu *et al*. 2012; Shad *et al*. 2014

which confer its claimed antioxidant, anticarcinogenic, and chemopreventive effects (Manchali *et al.* 2012; Pereira *et al.* 2011). The aerial parts of oregano (*Origanum vulgare* L.), prepared in infusions, decoctions or hydromethanolic extracts (80%), have antioxidant and antimicrobial potential probably related to flavonoids and phenolic acids (Martins *et al.* 2014).

Today, aggressive marketing highlighting the health-promoting benefits of mangosteen, acai, acerola or goji berry, among other fruits, bulbs, roots, seeds or leafy vegetables presented in Table 9.1, has resulted in their classification as "superfruits" or "superfoods." Scientific research carried out in recent years proves their effectiveness as healthy foods, and due to high profits, the food and pharmaceutical industries are increasingly interested in developing new products based on these plants.

However, in addition to edible plant parts, wild nonedible parts or plants can also be used as a source of health-promoting ingredients. Thus, medicinal and aromatic plants play an important role in the development of new or improved functional foods, as well as nutraceuticals. At the research level, some wild plant extracts are being incorporated into food products to increase their health-promoting properties. Martins *et al.* (2014) formulated new yogurts based on phenolic extracts of wild blackberry (*Rubus ulmifolius* Schott) flowers. The authors microencapsulated the hydroalcoholic extract in an alginate-based matrix and incorporated this into a yogurt to achieve antioxidant benefits. Recently, Caleja *et al.* (2015) improved the antioxidant properties of cottage cheese by the incorporation of fennel (*Foeniculum vulgare* Mill.) decoction (phenolic-enriched extract), improving not only functionality of the final product but also preservation effectiveness due to the antimicrobial potential of fennel.

Carocho *et al.* (2015a) transformed the Portuguese "Serra da Estrela" cheese into a functional food by incorporating dried chestnut (*Castanea sativa* Mill.) flowers or lemon balm (*Melissa officinalis* L.) plants, as well as their decocted extracts. The functionalized cheeses showed higher antioxidant activity, especially lipid peroxidation inhibition, bringing benefits both for consumers (healthier product) and producers (added-value product). The same authors also functionalized the Portuguese traditional cakes "económicos" by incorporation of dried chestnut (*C. sativa*) flowers or decoctions prepared from them (Carocho *et al.* 2015b). The final product showed increased antioxidant activity and phenolic content, without causing visible changes in inner and outer appearance.

9.3 Wild Plant-Based Nutraceuticals

9.3.1 The Emerging Concept and Applications of Nutraceuticals

A new generation of processed food is coming, which is a controversial subject for many people. Nutraceutical products represent a fast-growing sector within the food industry, aiming to increasingly attract the buyer to consume these novel dietary supplements and phytotherapeutic products. It is expected that in the near future, "food for special dietary needs," such as soups, smoothies, processed meat, bread and sausages, among others, will be enriched with nutraceutical formulations (Andlauer & Furst 2002; Regulation (EC) No. 2002/46).

Nutraceuticals can be defined as diet supplements that contain bioactive compounds or extracts, prepared from raw natural matrices that will provide a higher dosage that could not be obtained from normal food products and functional foods (DeFelice 1992; Espín *et al.*, 2007; Zeisel 1999). Directive 2002/46/EC of the European Parliament and Council, on the approximation of laws of Member States relating to food supplements, defines “food supplements” as foodstuffs with the purpose of supplementing the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, such as capsules, pastilles, tablets, pills, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities (Regulation (EC) No. 2002/46).

The health industry is using nutraceutical formulations as complements to prevent some diseases. Some authors have stated that any food or parts of foods can be considered nutraceutical compounds, as long as their beneficial health and nutritional claims are proved scientifically (Braithwaite *et al.*, 2014; McNamara, 1997; Ross, 2000). On the other hand, Gulati and Ottaway (2006) and Espín *et al.* (2007) distinguished nutraceuticals as components that are often consumed in unit dose forms such as tablets, capsules or liquids. They can be isolated nutrients or herbal products presented in pharmaceutical forms or processed products like cereals, smoothies, and soups for special diet requirements (Andlauer & Furst 2002; Braithwaite *et al.* 2014; Regulation (EC) No. 2002/46).

The concept of nutraceuticals is relatively recent, only appearing in the 1990s with the first publications and patents related to the subject (Figure 9.1). However, the increasing number of publications from academics (through articles and reviews) and industry (through patents) is notable. This can be explained by the fact that there is increasingly market demand for new, better, and safer food products. However, regarding plant-based nutraceuticals, the number of articles (and reviews) and patents is very low (see Figure 9.1) although it is growing. Many of the primary studies on nutraceuticals were made with individual compounds with known beneficial effects, but there is now interest in exploring the synergisms existing within plant extracts and incorporating them into nutraceuticals or modified functional food.

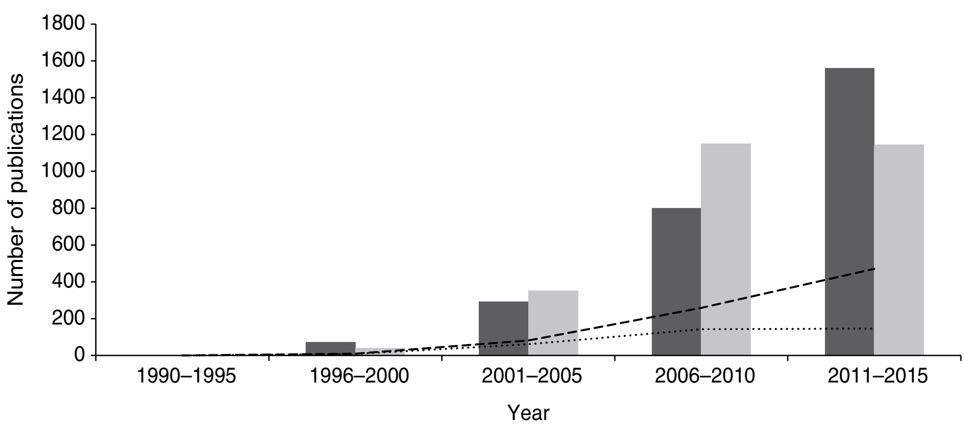

Figure 9.1 Number of research articles and reviews (■ and - - -), and patents (■ and ....) published in the period from 1990 to 2015 regarding nutraceuticals and nutraceuticals formulated with plant material, respectively (obtained on Web of Science, January 2015; keyword: nutraceutical; nutraceutical + plant).

Therefore, the development of legislation that regulates the production of nutraceutical formulations, their labeling and market supply is crucial. In January 2002, the European Food Safety Authority (EFSA) established Regulation (EC) No. 178/2002, setting down the general principles and requirements for food law. This Regulation also contains procedures for food safety, increasing the health protection of consumers. These guidelines are applied to all food products, including those with added functional properties, such as nutraceuticals and functional foods. From the perspective of the global pharmaceutical and medical industry, nutraceutical products are dietary supplements (Kwak & Jukes 2001). Specific regulation of nutraceutical products is still very patchy; in European law they have no specific category, being considered under the same parameters used for dietetic foods, dietetic supplements, and food supplements (Coppens *et al.* 2006; Regulation (EC) No. 2002/46) or even under medicinal classification (Gulati & Ottaway 2006). In the USA, nutraceuticals are considered only as dietary supplements (Bernal *et al.* 2011; Espín *et al.* 2007). The differences between European and USA regulation may be due to cultural, historical, and traditional backgrounds (Gulati & Ottaway 2006). However, the development of specific legislation in Europe is necessary to ensure food safety for consumers and to prove that nutraceuticals are safe and scientifically accepted, and this may dictate the future success of these products (Braithwaite *et al.* 2014; Byrne 2003).

Recent research has shown very promising prospects for different natural ingredients added to food products, creating benefits for consumers' health and added value for manufacturers (Coppens *et al.* 2006). Many of the published papers on nutraceuticals are focused on their beneficial health properties (Bernal *et al.* 2011), for instance their ability to decrease the development of heart disease (Garcia-Rios *et al.* 2013; Giordano *et al.* 2012; Izzo *et al.* 2010; Scicchitano *et al.* 2014) such as hypercholesterolemia (Mannarino *et al.* 2014), and also for the prevention and treatment of prostate cancer (Li *et al.* 2014b). Nutraceutical formulations have been proved to be safe and well tolerated, but further studies are required to assess the decreasing of secondary effects of nutraceuticals when compared to analogue commercial drugs for the treatment of certain diseases (Bernal *et al.* 2011; McAlindon 2006).

9.3.2 Recent Advances in Formulations for Nutraceuticals

Due to the difficulty in the classification of nutraceuticals, we are faced with two types of products: nutraceuticals in the form of dietary supplements (tablets, capsules, solutions, syrups, powders, chewing tablets, among others) and those in the form of free or encapsulated extracts/compounds to be inserted into a food matrix (i.e. used to develop functional foods). For that reason, the formulation of nutraceuticals involves a wide range of methodologies and techniques, from the most used (tableting) to the newest and most advanced, such as microencapsulation complemented with nanotechnology.

First, it is necessary to ensure the safety and quality of the nutraceutical product. The chemical, nutritional, and bioactive characterization of the compound/extract that will be part of the formulation is required, as well as control of the dosage. For this, some advanced analytical techniques are used such as mass spectrometry (MS), nuclear magnetic resonance (NMR), high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), and gas chromatography (GC), among others (Bernal *et al.* 2011; Sener & Orhan 2005).

The vast majority of nutraceutical formulations are designed for oral administration. Braithwaite *et al.* (2014) reported a description of some new nutraceutical formulation strategies to improve dosage, design, and delivery of the bioactives. From liposomal carriers, electrospun fiber mats, microsponges and nanoesponges, cyclodextrin complexations to biodegradable hydrogels, all these technologies prove the importance of nutraceuticals in today's economy, with a growing investment by the industry in new formulations that respond to market demand. Second-generation nanocrystals, another new formulation, are an emerging technology for the delivery of poorly soluble bioactives. They are mostly used for drug delivery to solve poor solubility and bioavailability. However, they also represent a reliable response for the delivery of many nutraceutical compounds already on the market, such as antioxidants. The main advantage of nanocrystal systems is the capacity to be applied via oral, intravenous, dermal, mucosal, ocular and even pulmonary routes (Shegokar & Müller 2010).

It is important to realize that nutraceutical formulations go far beyond diet products or products enriched with a certain bioactive compound. Formulations are already on the "micro" and "nano" scales, which can be incorporated in food matrices but also in pharmaceutical formulations, serving as a complement to traditional medicine. Microencapsulation complemented with nanotechnology appears to overcome problems related to the use of free bioactives but also to provide controlled target delivery release (Braithwaite *et al.* 2014; Dias *et al.* 2015 Ezhilarisi *et al.* 2013; Huang *et al.* 2010b). Nanoscale delivery systems have the advantages of improving solubility, masking undesirable flavors and smells, and preventing the degradation of the bioactive compounds; they provide a triggered controlled release and, most important of all, increased bioavailability by prolonging contact within the gastrointestinal tract (Cerqueira *et al.* 2014). Microemulsions, for instance, are one of the most used techniques for the solubilization and transport of water and oil-insoluble compounds, presenting easier formulation and manufacture and also high stability during storage (Spernath & Aserin 2006).

Food protein-based materials can also be used at "micro" and "nano" scales, depending on the type of encapsulation methodology used to produce the capsules and also the objective of the work. Proteins present the ability to form gels and emulsions due to their functional properties, which makes them appealing to the industry and academia for the encapsulation of nutraceuticals (Chen *et al.* 2006). Hydrocolloids fibers are being proposed to encapsulate nutraceutical compounds and extracts; they are nontoxic, inexpensive, and generally recognized as safe (GRAS). Furthermore, since they are complex carbohydrates, consumption on a regular basis showed health benefits for cardiovascular disease and diabetes (Janaswamy & Youngren 2012). Researchers are also developing formulations linking nutraceuticals with drugs to enhance efficacy and reduce dosage and side-effects of chemical compounds (Braithwaite *et al.* 2014).

9.3.3 Examples of Nutraceuticals Based on Wild Plants

For economic and ecological sustainable reasons, the FAO recommends the cultivation of medicinal and aromatic plants that represent a genetic pool of raw material with better control of biotic and abiotic factors, allowing the standardization of the final product (Schippmann *et al.* 2002). For that reason all the listed examples in Table 9.2 are

Table 9.2 Nutraceutical formulations based on plants with traditional wild use.

Plant species	Used part	Extract	Formulation	Application	Available commercial product	Reference
Abelmoschus manihot L.	–	Standardized extract	Pills	Renal inflammation, glomerular; chronic kidney disease	–	Tu *et al.* 2013
Artemisia annua L.	Leaves	Dried leaves	Tablet	Antimalarial drug	–	Weathers & Towler 2014
Berberis aristata D.C.	Root	Standardized extract	Tablet	Glycemia and lipid alteration	Berbenol®	Pierro *et al.* 2013
Silybum marianum (L.) Gaertn.	Fruit					
Boswellia serrate Triana & Planch.	–	Gum extract	Pills	Osteoarthritis	5-Loxin®	Sengupta *et al.* 2010
	–	Gum extract + essential oil	Pills	Osteoarthritis	Aflapin®	Sengupta *et al.* 2010
Cajanus cajan L.	Seed		Syrup	Sickle cell anemia	Ciklavit®	Imaga *et al.* 2013
Commiphora angolensis Welw.	Roots	Aqueous extract	Syrup, Pills	Antihepatocellular carcinoma	–	Pereira *et al.* 2013b, 2014
Cucumis melo cantalupensis	Fruit	Juice	Pills	Stress and fatigue	Extramel®	Milesi *et al.* 2009
Cynara scolymus L.	Leaves	Aqueous extract	Syrup, Pills	Antihepatocellular carcinoma	–	Pereira *et al.* 2013b, 2014
Echinacea angustifolia (D.C.) Hell.	Root	Polysaccharide extract	Syrup	Immunomodulatory effect	Polinacea®	Dapas *et al.* 2014
Echinacea purpurea (L.) Moench	Leaves and root	Dried leaves and roots	Pills	Cold	Echinaforce®	Brinkeborn *et al.* 1989

Echinacea purpurea (L.) Moench *Echinacea angustifolia* (D.C.) Hell.	Root	Ethanolic extract	Tablet	Bioavailability of bioactive compounds	–	Matthias *et al*. 2007
Echinacea purpurea (L.) Moench *Glycyrrhiza glabra* L.	Root	Standardized extract	Tablet	Immunological effects	Revitonil®	Wagner & Jurcic 2002
Ficus carica L.	Fruits	–	Syrup	Bioactive compounds	–	Puoci *et al*. 2011
Gingko biloba L.	Leaves	Aqueous extract	Syrup, Pills	Antioxidant activity	–	Pereira *et al*. 2013a
	Leaves	–	Tablet	Mild cognitive impairment	–	Bäurle *et al*. 2009
Gingko biloba L. *Panax ginseng* sp.	Leaves Root	Standardized extract	Pills	Mild cognitive impairment	Memo®	Yakoot *et al*. 2013
Ginseng panax sp.	Root	Standardized extract	Tablet	Antiaging	Eufortyn®	Xu *et al*. 2010
Hedera helix Linné L.	Leaves	Dry leaves	Tablet	Cough	Prospon®	Stauss-Grabo *et al*. 2011
Hypericum perforatum L.	Shoot tips	–	Tablet	Depression	–	Lenoir *et al*. 1999
Juglans regia L.	Leaves	Ethanolic extract	Pills	Hyperglycemia	–	Hosseini *et al*. 2014
Magnolia officinalis Rehder & Wilson *Phellodendron amurense* Rupr.	Bark	Standardized extract	Pills	Reducing stress and anxiety	Relora®	Talbott *et al*. 2013
Mikania laevigata Willd.	–	–	Syrup	Antispasmodic and respiratory diseases	–	Graça *et al*. 2007
Murraya koenigii (L.) Sprengel *Tribulus terrestris* L.	Leaves	Standardized extract	Pills	Benign protastic hyperplasia	–	Sengupta *et al*. 2011

(*Continued*)

Table 9.2 (Continued)

Plant species	Used part	Extract	Formulation	Application	Available commercial product	Reference
Peumus boldus L.	Leaves	Dried leaves	Tablet	Choleretic, diuretic, stomachic, cholagogic properties	–	Palma *et al.* 2002
Phellodendron amurense Rupr.	Bark	Standardized extract	Pills	Joint pain and movements	–	Oben *et al.* 2009
Citrus sinensis (L.) Osbeck	Peel	–	–	–	–	–
Phoenix canariensis Chabaud	Sap	–	Syrup	Sugar and nutritional source	–	Luis *et al.* 2012
Phyllantus amarus Schum. & Thonn	Leaves and stems	–	Syrup	Antitussive	–	Avbunudiogba *et al.* 2013
Proposis pods L.	Fruit	–	Syrup	Bioactive compounds	–	Quispe *et al.* 2014
Salvia officinalis L.	Leaves	Ethanolic/water extract	Pills	Glycemia	–	Kianbakht & Dabaghian 2013
Silybum marianum (L.) Gaertn.	Bark	Aqueous extract	Syrup, Pills	Antihepatocellular carcinoma	–	Pereira *et al.* 2013b, 2014
Smallanthus sonchifolius Poepp. & Endl	Root	–	Syrup	Obesity and insulin resistance	–	Genta *et al.* 2009
Uncaria tomentosa (Willd.) D.C.	Bark	Aqueous extract	Pills	Macrophage resistance	–	Lenzi *et al.* 2013
Vitis vinifera L. cv. *Cabernet sauvignon; Vitis vinifera* L. cv. *Merlot*	Grape	–	Tablet	Bioavailability of resveratrol	–	Ortuño *et al.* 2010

plants that are normally consumed as wild and that present some bioactive properties, allowing the development of nutraceutical formulations. In this chapter, we only discuss nutraceutical formulations in the form of dietetic supplements (capsules, tablets, syrup). A detailed description of microencapsulated nutraceuticals based on plants has been previously provided by Dias *et al.* (2015), where the most frequently used microencapsulation techniques and materials are described, and also the most common extracts and bioactive compounds, including also some applicability studies for the developed microcapsules (e.g. milk, cheese, yogurt, ice cream, pasta, meat, bread, and chewing gum enhanced with bioactive extracts of plant origin).

Currently, some trademarked plant-based nutraceuticals are used as adjuvants in several illness processes. For instance, Ciklavit® is a syrup which has effects again sickle cell anemia, prepared with an aqueous extract of *Cajanus cajan* L. seed, a plant found in semiarid tropical regions, commonly consumed in soups and rice dishes (Imaga *et al.* 2013). Xu *et al.* (2010) studied the effect of a commercial product, Eufortyn®, that comprises chemical compounds including terclatrated coenzyme Q_{10} and creatine, but also an extract of *Ginseng panax* sp. roots, which has shown effects in the antiaging process of rats. The roots of *Echinacea purpurea* (L.) Moench and *Glycyrrhiza glabra* L. are the major constituents of a commercial tablet, Revitonil®, used mainly for its immunological effects, while the leaves of *Hedera helix* L. are used in Prospon®, marketed for cough symptoms (Stauss-Grabo *et al.* 2011; Wagner & Jurcic 2002). Extramel® consists of small pills of melon juice (*Cucumis melo* var. *cantalupensis* Naudin) used to treat stress and fatigue symptoms (Milesi *et al.* 2009), while 5-Loxin® and Aflapin® contain gum extract and gum extract plus oil, respectively, of *Boswella serrata* Triana & Planch, being used for osteoarthritis (Sengupta *et al.* 2010).

The genus *Echinacea* is well known for its medicinal properties. Brinkeborn *et al.* (1989) reported the effects of pills (Echinaforce®) prepared from *E. purpurea* roots and leaves in the treatment of the common cold, while Dapas *et al.* (2014) studied the root syrup (Polinacea®) obtained using *E. angustifolia* (D.C.) Hell. for its immunomodelatory effects. Berbenol®, a tablet formulation made from an extract of *Berberis aristata* D.C. and *Silybum marianum* (L.) Gaertn., taking advantage of the synergistic effects of both plants, is used for the treatment of glycemia and lipid value alterations in patients with type 2 diabetes (Pierro *et al.* 2013).

However, most of the formulations reported in the literature as nutraceuticals do not reach the market due to a lack of more in-depth studies, including clinical trials, or for legal or technical reasons. Lenoir *et al.* (1999) tested the effects of tablets containing three different concentrations of shoot tips from *Hypericum perfuratum* L. on symptoms in patients with mild to moderate depression. The bark of *Phellodendron amurense* Rupr., traditionally used in Chinese medicine, and the peel of *Citrus sinensis* (L.) Osbeck were inserted into pills in order to evaluate their beneficial effects in joint pain; both species contributed to weight loss in tested patients and also an improvement in their health status (Oben *et al.* 2009). The leaves of *Murraya koenigii* (L.) Sprengel and *Tribulus terrestris* L. are traditionally used in India for curry and to treat infertility and impotence, respectively. Sengupta *et al.* (2011) studied the effects of both plant pills in benign prostatic hyperplasia, obtaining satisfactory results.

Type 2 diabetes is increasing worldwide; moreover, the additional health problems related to this disease are also an important concern. Kianbakht and Dabaghian (2013) reported the effects of pills prepared from *Salvia officinalis* L. leaves in patients with type 2 diabetes and hyperlipidemia, describing good results in contrast to the placebo group, and without adverse side-effects. Furthermore, Hosseini *et al.* (2014) proved the effectiveness of pills obtained from *Juglans regia* L. leaves in patients with type 2 diabetes. Genta *et al.* (2009) studied humans given "yacon" syrup obtained from the roots of *Smallanthus sonchifolius* Poepp. & Endl with a high fructooligosaccharide content, demonstrating beneficial health effects in insulin-resistant patients.

Age-related cognitive changes and dementia are also a worldwide concern. *Gingko biloba* L. leaves have been described as being able to affect some neurological properties. Bäurle *et al.* (2009) studied the effects of tablets made from the extract of this plant in mild cognitive impairment; the authors reported the nutraceutical as safe, effective, and acting as an adjuvant to patients who suffer from this illness. There is already on the market a product, Memo®, prepared from *G. biloba* leaves and *Panax ginseng* sp. roots, used against mild cognitive impairment, by slowing the cognitive decline that occurs during the aging process (Yakoot *et al.* 2013). Cognitive wellbeing is also related to stress, depression, and fatigue, and the methods used to treat stress conditions range from a balanced nutritional plan to powerful drugs such as benzodiazepines. Relora® is a pill formulation consisting of a blend of bark extracts of *Magnolia officinalis* Rehder & Wilson and *P. amurense* standardized to honokiol and berberine, respectively, used in the treatment of stress and anxiety; the results achieved in a clinical trial performed by Talbott *et al.* (2013) showed that the combination of these two plants improved a variety of mood state parameters, lowering fatigue and increasing vigor.

Current stress-related diseases are a direct consequence of our modern lifestyle; the human organism produces reactive oxygen species, which are related to higher incidences of cardiovascular, brain, and immune system diseases (Carocho & Ferreira 2013b). Therefore, nutraceutical formulations are also being studied for their antioxidant properties, such as the syrup obtained from the fruits of *Ficus carica* L. and *Prosopis* pods, both widely used in traditional cuisine to prepare desserts and sweets (Puoci *et al.* 2011; Quispe *et al.* 2014). Furthermore, the syrup and pills prepared from *G. biloba* leaves, known for their action against degenerative neurological diseases, as previously mentioned, but also for their action in the cardiovascular system and cerebral vascular activity, were studied for their antioxidant capacity, showing higher activity than the corresponding infusion and extract; this higher activity was attributed to the highest content in phenolic compounds (Pereira *et al.* 2013a). Pereira *et al.* (2013b, 2014) also tested different nutraceutical formulations (pills and syrup) prepared using *Cynara scolymus* L., *Cochlospermum angolensis* Welw., and *S. marianum*, known for their capacity to prevent oxidative stress and liver disease, in terms of antioxidant and antihepatocellular carcinoma activities; the synergistic effects between these nutraceuticals (mixtures) were also assessed, showing many advantages over individual components.

The bioavailability of nutraceutical formulations is also a hot research topic as metabolic reactions can decrease their bioactive properties. There are already some studies in this direction, such as the one conducted by Matthias *et al.* (2007) on liquid (alcoholic solution) and tablet formulations prepared with *E. purpurea* and *E. angustifolia* roots. Alkylamides, found in both species, were used as target compounds to evaluate the nutraceuticals' bioavailability; these compounds were rapidly and easily absorbed in both formulations. A similar study was performed with tablets prepared with red wine grape extracts made from *Vitis vinifera* L. cv. *Cabernet sauvignon* and *Vitis vinifera*

L. cv. *Merlot*, in order to assess the bioavailability of resveratrol; however, in this case the bioavailability was higher in the natural matrix than in the nutraceutical formulation (Ortuño *et al.* 2010).

Nutraceuticals can also combine plant-based principles with other natural matrices such as mushrooms. A good example is ASHMI^{TM}, a pill formulation use in asthma treatment, containing the plants *Sophora flavescens* Aiton and *glycyrrhiza uralensis* Fisch. (root aqueous extracts) and the mushroom *Ganoderma lucidum* (Curtis) P. Karst. (fruiting body aqueous extracts) (Kelly-Pieper *et al.* 2009). Wong *et al.* (2004) also studied the effects of *Coriolus versicolor* (L.: Fr.) Quél. and *Salvia miltiorrhiza* Bunge pills (polysaccharides extract) on the improvement of cellular immunity in healthy subjects, which proved to be effective and without adverse effects.

9.4 Wild Plant-Based Drugs

9.4.1 From the Bioactive Phytochemical to the Active Principle

Plants have been used as medicine by humans for thousands of years, since their first use as teas, tinctures, poultices, etc. to the isolation of morphine from opium in the early nineteenth century. Since then, administration methods have changed drastically (Balunas & Kinghorn 2005; Newman *et al.* 2000). Today, there are many sources of new bioactive compounds, including plants, bacteria, fungi, and marine organisms; in fact, from 1981 to 2002, 61% of the 877 new small molecule chemical compounds were derived from natural products, and in specific therapeutic areas (antibacterial, antifungal, antiparasitic, and antiviral treatments), these compounds have provided 70% of total drugs (Cechinel-Filho 2012). There are six classes of compounds that result from botanical sources:

- bioactive compounds that are used directly as drugs, as in the case of digoxin, used for heart conditions
- bioactive compounds with structures that may act as lead compounds to more potent drugs, for instance, paclitaxel, a mitotic inhibitor used in cancer chemotherapy
- chemophores, which are cells that transduce energy, and may be converted into druggable compounds
- pure phytochemicals that can be used as markers to standardize crude plant material
- phytochemicals that can be used as pharmacological tools
- herbal extracts as botanical drugs or green tea extracts (Katiyar *et al.* 2012).

Although there are numerous classes of compounds and methods of obtaining them, the pharmaceutical industry faces unprecedented challenges, with fewer compounds being found, tested, and released to the public. Typically, after *in vitro* assays showing bioactivity of a specific compound, it may start preclinical studies on animal models followed by a "New Drug Application" addressed to the FDA (USA) and EFSA (EU). If approved, the human studies take place, divided into three phases with escalating numbers of participants to determine the toxicity, side-effects, and other effects not detectable in animal models. The ideal approval process of a new drug is hardly ever linear, and several drawbacks ensue, meaning that several years to some decades may elapse before a compound is marketed as a drug (FDA 2014; Paul *et al.* 2010). Compounds leading to hypothetical drugs must achieve suitable solubility and chemical stability, demonstrate effectiveness in animals (adequate pharmacological profile) and satisfactory bioavailability (with a good half-life), the interactions with cytochrome p450 (CYP450) must be clarified and finally, there must be no obvious toxicity (Cechinel-Filho 2012).

With the reduction of new compounds appearing as potential drugs, humans have once again turned to Nature in order to mitigate the relative void of combinatorial chemistry to find new compounds (Phillipson 2007). The quest for compounds in plants can be carried out in many ways.

- Random selection followed by chemical screening (simple tests that may lead to false positives and false negatives, rendering conclusions difficult to assess and the class of compounds responsible for the activity impossible to specify).
- Random selection followed by one or more biological assays (carried out in animals or *in vitro* assays that screen high volumes of plant species in order to find new drugs).
- Follow-up of biological activity reports (reports of plant extracts with interesting biological activity, which were not studied for their active principles).
- Follow-up of ethnomedical (traditional medicine) uses of plants – plants used in traditional systems like Ayurveda, Unani, Kampo, and traditional Chinese medicine which are not seen as credible by Western scientific methods and are harder to assess, but their undeniable results in many illnesses are impossible to overlook. Herbalism, folklore, and shamanism, which are also viewed with scepticism, are also considered due to their strong reliance on endemic plants.
- Use of databases (large literature sources systematically organized that allow correlation of ethnomedical practices with experimental biochemical and pharmacological activities or to identify plants with multiple effects) (Fabricant & Farnsworth 2001).

To achieve the final compound, a large number of molecules must be extracted from the medicinal plant through various methods.

- Percolation, used for poorly soluble plants or when the price of the plant is relevant. The matrix is placed in a container with solvent flowing through it.
- Countercurrent extraction is obtained by moving solvent through the raw plant in countercurrent.
- Supercritical fluid extraction is carried out by placing the raw plant in a container and filling it with supercritical fluid until the pressure and temperature rise by a considerable amount. These conditions help the fluid to achieve a very high solubility capacity, extracting the compounds of interest.
- Microwave-assisted extraction relies on microwaves that extract compounds more selectively and rapidly while depending less on solvents.
- Maceration is the process of placing the raw plant in a container for different periods of time, while kinetic maceration uses the same process but the mixture is maintained under constant stirring.
- Turbo-extraction uses a cold solvent at high sheer forces, which leads to particle reduction, cell disintegration, and temperature increase.
- Decoctions and infusions rely on hot water as the extractor. Infusions are prepared by adding the plant to boiling water, and maintaining it for 5–10 minutes, while decoctions are prepared by adding the plant to cold water and heating it until it boils, maintaining it for 5–10 minutes.

- Soxhlet extraction relies on cycles of extraction within a glass chamber in which the solvent boils and condenses back into contact with the plant. After filling the chamber it is unloaded into a glass recipient that is heated, evaporating the solvent, only to condense back into the chamber, in a cyclical way.
- Sublimation extraction sublimes the compounds of interest leaving behind impurities which then condense in another chamber.
- Steam distillation relies on steam to carry the compounds from the boiling mixture containing the plant which then condenses.
- Ultrasonic-assisted extraction is used to increase mass transfer between the plant material and a solution by inducing liquid circulation and turbulence (Cechinel-Filho 2012; Sarker & Nahar 2012; Sticher 2008).

After extraction, the solutions have to be screened to determine their constituents and dereplication (which is the process that recognizes previously studied components that are not important for a screening of new ones) to then prepare for separation and isolation. To separate and isolate the mixtures into their constituents, several methods are used; HPLC is the simplest and can yield results in a short time without needing derivatization steps, although the results can be poor in resolution, and confusing. Ultra high-pressure liquid chromatography (UHPLC) is an improvement on HPLC by enhancing the resolution and throughput for rapid fingerprinting of crude extracts. Liquid chromatography coupled to a photo diode array (LC-PDA) detector is another add-on to a HPLC by allowing a view of the UV spectra, which is useful for detecting compounds with characteristic chromophores. HPLC-MS is HPLC that is coupled to a mass spectrometer, aiding detection, quantification, and identification by providing at the same time a chromatographic (retention times) and a mass spectrometric (m/z) dimension. HPLC-NMR is one of the strongest HPLC methods used to separate compounds. It has the advantage of not relying on commercial databases for spectral comparison, like HPLC-MS. HPLC-NMR provides structural information or even stereochemical information, as well as detection of any hydrogen-containing compounds. LC-SPE-NMR uses a solid-phase extraction coupled to a HPLC and finally a NMR detector, and allows the NMR detection after HPLC separation by either trapping the peaks on SPE or by HPLC microfractionation, drying, and reinjection of the concentrated peak in a microflow capillary LC-NMR probe. Microflow NMR and cryogenized probes are derivations of this technique (Cechinel-Filho 2012).

It is incontestable that medicinal plants provide unlimited opportunities for new drug discovery because of the unmatched availability of chemical diversity. Nevertheless, since bioactive phytochemicals occurring in plant materials consist of multicomponent mixtures, their extraction, separation, and isolation still create problems. In fact, extraction techniques can negatively affect the integrity of active principles, and practically all of them have to be purified by the combination of several chromatographic techniques or various other purification methods. Thus, it is expected that improvements in these methods will allow us to overcome some of the current limitations, as well as driving the development and introduction of new technologies.

9.4.2 Common Formulations in Drugs from Plant Origin

Drug development has evolved steadily since it first began as part of traditional medicine, and today more and more plant compounds are used as precursors, prototypes, and probes in drug production (Ramawat & Mérillon 2008). Depicted in Table 9.3 are

Table 9.3 Drugs derived from natural products.

Plant of origin before modification	Used part	Active principle	Application	Reference
Artemisia annua L.	Aerial parts	Artemisinin	Antimalarial	Phillipson 2007
Atropa belladonna L.	Aerial parts	Tiotropium	Chronic obstructive pulmonary disease	Balunas & Kinghorn 2005
	Aerial parts	Atropine	Mydriatic agent, antispasmodic	Ramawat & Mérillon 2008
Betula spp. L.	Bark	Betulinic acid	Melanoma, anticancer, antimalarial, anti-HIV, anthelmintic, antiinflammatory, antiretoviral	Balunas & Kinghorn 2005; Ramawat & Mérillon 2008
Callistemon citrinus Curtis	Aerial parts	Nitisinone	Tyrosinemia	Balunas & Kinghorn 2005
Calophyllum lanigerum W.	Aerial parts	Calanolide	Anti-HIV	–
Camptotheca acuminata Decne	Bark and stem	Camptothecin	Anticancer	Phillipson 2007
	Bark and stem	Topotecan	Metastic ovarian cancer	–
	Bark and stem	Irinotecan	Colorectal cancer	–
	Bark and stem	Exatecan	Anticancer agent	Balunas & Kinghorn 2005
Capsicum spp. L	Fruit	Capsaicin	Osteoarthritis, psoriasis, diabetic, neuropathy	Ramawat & Mérillon 2008
Catharanthus roseus L.	Aerial parts	Vindesine	Leukemia and lung cancer	Phillipson 2007
	Aerial parts	Vinorelbine	Breast cancer	–
	Aerial parts	Vinflunine	Anticancer agent	Balunas & Kinghorn 2005
Chondrodendron tomentosum Ruiz & Pavón	Aerial parts	Tubocurarine	Neuromuscular blocking agent	Phillipson 2007
Combretum caffrum (Eckl. & Zeyh.) Kuntze	Aerial parts	Combretastatin A4 phosphate	Anaplastic thyroid cancer	Ramawat & Mérillon 2008
Dioscorea genus	Tubers	Diosgenin	Contraceptive	–
Erythroxylum pervillei Bail	Stem bark	Pervilleine A	Epidermoid cancer	Balunas & Kinghorn 2005

Euphorbia peplos L.	Sap	Ingenol 3-angelate	Skin conditions	Ramawat & Mérillon 2008
Galanthus woronowii Losinsk.	Bulbs and flowers	Galantamine	Alzheimer's	Balunas & Kinghorn 2005
Galega officinalis L.	Aerial parts	Guanidine derivatives	Type 2 diabetes	Ramawat & Mérillon 2008
Glycine max L. Merril	Aerial parts	Phenoxodiol	Cervical, ovarian, prostate, renal, and vaginal cancer	–
Huperzia serrata Thunb. (Ex Murray) Trevis	Aerial parts	Huperizine	Alzheimer's	–
Illicium verum Hoof f.	Fruit	Oseltamivir phosphate (Tamiflu)	Influenza	–
Panax ginseng L.	Aerial parts	Protopanaxadiol	Apoptotic effect in cancer cells	–
Papaver somniferum L.	Seed pods	M6G	Pain medication	Balunas & Kinghorn 2005
	Seed pods	Apokyn	Parkinson's	Ramawat & Mérillon 2008
Podophyllum peltatum L.	Root	Etoposide	Small cell lung cancer, lymphomas, testicular cancer	Phillipson 2007
	Root	Teniposide	Brain tumors	–
Physostigma venenosum Balf.	Seed	Physostigmine	Parkinson's	–
Plectranthus barbatus Andrews	Aerial parts	Colforsin daropate	Anticancer	Butler 2005
Taxus brevifolia Nutt.	Bark	Taxol	Anticancer chemotherapy	Phillipson 2007
	Bark	Taxotere	Breast cancer and nonsmall cell lung cancer (adjuvant)	–

some of the most important drugs either developed using compounds derived from plants, or synthetic ones that were inspired by them, along with the plant from which they were first isolated and the illnesses they are used for. The recent change of attitude from big pharmaceutical companies, which are starting to look for natural compounds, has been a major tonic in the industry, helping to develop new drugs. The applications of natural compounds for human health are endless, and considering that currently only one-quarter of flowering plants is used, there is hope of finding treatments and solutions for many patients around the world (Lange 2004).

The WHO reports that over 21 000 plant taxa are used for medicinal purposes, although this number does not include cosmetics, spirits, and aromas (FAO 2002; Lange 2004). Roughly 80% of developing countries depend on plant-based drugs, although the WHO suggests that in the near future a similar percentage of the entire world population will depend on them. Furthermore, 30% of the drugs sold worldwide contain products derived from plants (FAO 2005).

Of the global trade in medicinal plants, it is hard to know how much is represented by wild or cultivated ones. Although the pharmaceutical industry has isolated a large number of bioactive compounds from wild plants (edible and medicinal), there are considerable disadvantages in harvesting wild medicinal plants rather than cultivating them for industrial drug development. The pharmaceutical industry mainly uses cultivated plants as primary material, despite the expensive domestication and cultivation process, in order to obtain a standard and well-known source of the active principle, in the necessary amounts for industrial-level processing. Moreover, there are some disadvantages related to wild plant gathering, including uncontrolled harvest that leads to extinction of the plant and erosion of the ecosystem. Other problems include poor knowledge about the biology of the plants, little or no inventory, ownership conflicts of the harvest zones, and scarce income due to overharvesting. Cultivation in small farms and households or in large and extensive production facilities could be an alternative, although the disadvantages are still great, due to the large investments needed, the reduction of incentive to conserve native ecosystems, devaluation of wild plants, reduction of genetic diversity and the risk of the introduced plant becoming an invasive species (FAO 2002).

9.4.3 Wild Plant-Based Drugs for Different Therapeutic Targets

Wild plant-based drugs are everywhere; the definition of a drug is quite vague, encompassing all "chemical substances used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being." In this way, all molecules used by any type of medicine, modern or traditional, could be classed as drugs. To narrow down the results, only drugs used and approved in Western modern medicine are considered here, otherwise the list would be endless, although alternative medicines are quite well documented (Ahmad *et al.* 2006; Hawkins 2008; Osbourn & Lanzotti 2009; Trivedi 2009).

Medicinal plants represent 25% of prescription drugs in modern medicine. Of the 3000 plants traded for medicinal purposes, only 900 are cultivated, which means that 70–80% of the whole market depends on wild collection (Hawkins 2008). The conservation of habitats of these plants is the responsibility of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), which is the most important source of information on wild medicinal plants in use. *Galanthus* spp. L., an herbaceous plant endemic to the northern hemisphere, is the source of galanthamine, an approved drug used against Alzheimer's disease (Heinrich & Teoh 2004). *Taxus brevifolia* Nutt., the conifer that is the source of the anticancer agent Taxol®, also known as paclitaxel, is another success story of the medicinal power of plants, although it has endangered some cultivars of the tree. The alkaloid colchicine, derived from *Colchicum autumnale* L. corms, is used for the treatment of gout, under the name Colcrys (Romano 2013). The treatment of cardiac diseases also depends on compounds derived from wild medicinal plants, including digoxin, a cardiac glycoside extracted from the herb *Digitalis lanata* Ehrh. It is also marketed under the names Lanoxin®, Lanoxicaps®, Cardoxin® and Digitek®, among others (Hawkins 2008). The cinchona tree, *Cinchona officinalis* L., endemic to South America, is a natural source of quinine, a known antimalarial alkaloid that is used against this disease in modern medicine. There are reports of other uses of this molecule, which have recently been investigated (Christoforidis 2014). *Camptotheca acuminata* Decne is a tree native to China and Tibet which is rich in an alkaloid called camptothecin, used as an anticancer agent (Gaur *et al*. 2014). These examples illustrate some of the illnesses that can be cured or attenuated with wild plant compounds.

The endless combination of compounds found in nature that may have application in medicine provides hope for treatments of illnesses that have not yet been controlled or cured. The search to find new compounds continues at a steady pace and technology keeps lending precious help to this quest. Wild medicinal plants are today still as valuable as they were in the pre-modern medicine era. However, the pursuit of bioactive compounds should never overlook the habitats and wellbeing of the species. Research should continue to try and cultivate the plants that are not yet fit to be intensively grown, therefore reducing dependency on wild plants. But while there is no alternative, mankind should harvest them from nature, but always ensuring their continuity for generations to come.

9.5 Conclusion

Functional foods and nutraceuticals have been reported as one of the top trends of today's food industry. Apart from the naturally occurring functional foods, the development of new functional foods, nutraceuticals, and drugs based on plants is an active and very promising area of research, indispensable for the substantiation of health claims and benefits. The characterization of plant ingredients by advanced technologies, standardization of human clinical trials, and the use of emerging methodologies are crucial strategies for the development of new functional products and drugs. Additionally, the degree of acceptance and awareness of functional foods and nutraceuticals by consumers, the association between manufacturers and academic researchers, and the effects of new regulations for nutrition and health claims are crucial factors for future market evolution. Despite all the potential of these products to prevent diseases and promote human health, health professionals, nutritionists, and regulatory toxicologists should work together to plan appropriate regulation to provide the ultimate health and therapeutic benefit to humans.

However, due to the rising demand for plant-based functional foods, nutraceuticals, and drugs in higher quantities to promote health, longevity, and quality of life, wild harvested medicinal plants are taking on an increasing role and many of them have become endangered due to irresponsible collection, associated with economic interests. Therefore, the cultivation of these species is an alternative that needs to be taken into account. Furthermore, the next phase of market growth depends on valid scientific research for new product technologies, patents, more effective branding, and trademark strategies in product manufacture and international regulatory compliance.

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