7. MEDICINAL PLANTS

7.1. Medicinal plants and their bioactive compounds

7.1.1. Historical aspects

Historical and ethnographic data are a rich heritage that proves the long tradition of crafting, growing and manufacturing of medicinal plants used for multiple purposes in many countries since long time ago.

Thousands years ago the ancient Egyptians have discovered simple methods for plant extraction and knew how to use perfumes and fine oils (papyri since 2000 BC contained such proofs) as well as aromatic waxes for embalming.

Ancient Greek and Roman population knowledge about medicinal plants and their healing properties was registered in some ancient text books (*Hippocrates-500 BC, Galenius, Paracelsus)* and certain pharmacological and clinical effects to day were confirmed. In Romania, one of the first reference about the ancient population knowledge about herbs was Herodot (484-425 BC), who described how local people used herbs for wound repairing and pain release. Other documents (Ovidius, 100-105) and Dioscorides (who created the first collection of medicinal plants) proved that natural remedies were known and used by the inhabitants of the old territories of Romania (Onisei et al., 2006).

During the Middle Age period the use of medicinal plants was associated to magic, superstitions and different rituals, but the Renaissance knowledge accumulation supported herbs to recover their place in health maintaining. Plants were carefully crafted, dried and stored, being used at large scale for infusion, decoction and ointments preparation (traditional medicine products, which formula are still efficient).

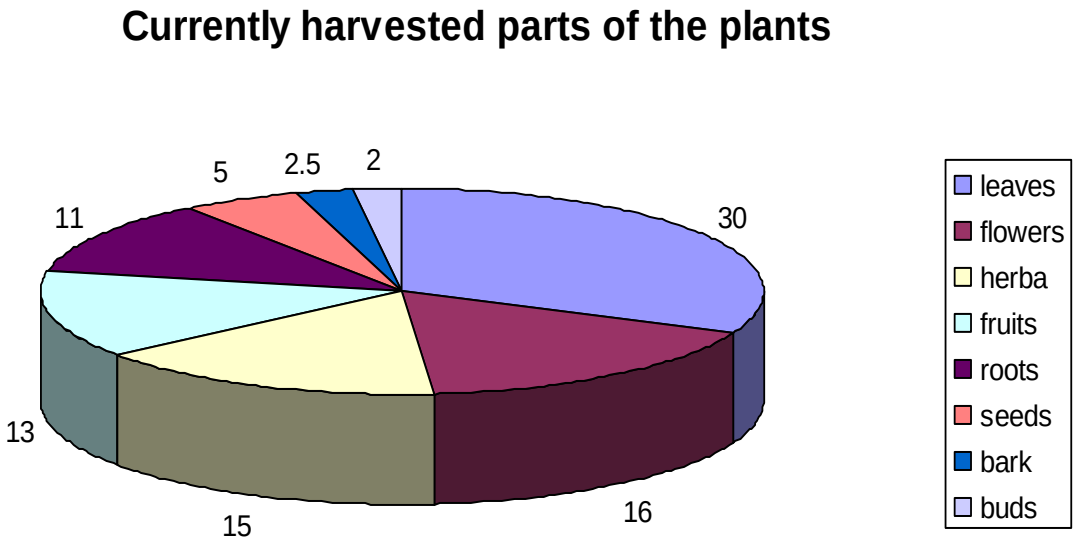
Due to the multiple forms of utilization of these valuable local bio-resources, several sciences were involved during the last centuries in the study of medicinal plants, their botanical, ecological, physiological aspects, chemical properties, economic importance, etc.

Herbs are well known sources of natural ingredients (vitamins and minerals, amino acids, fatty-acids, essential oils) and food additives (flavouring, colouring, preservative agents) in functional beverage and food industry. They are also used as culinary spices (in the gastronomy of different population) or raw material for herbal food supplements, a new category of products in increasing demand at global level.

It should also be noticed the high interest for body-care and cosmetic natural products based on plant extracts, aromatherapy (essential oils combination for different purposes) and other purposes (honeydew, pollen and propolis producing species) or ornamental (in landscaping).

Romanian wild flora, for example (near 3700 higher plant species), has about 700 medicinal plants traditionally used in folk medicine (Pârvu,1991), out of which 324 species scientifically proved to have therapeutic properties and 180 species can be used at industrial scale for plant extraction and different manufactured natural products. It should be noticed that more than hundred species have dyeing properties. They contain very resistant, bio-degradable pigments, used in food industry as colouring agents ("digestive pigments"), cosmetic (hair care) or natural fibres dyeing (especially wool and cotton). There are also 40 valuable species due to their content in tannin (accumulated in bark, wood, leaves or fruits) and resins (mainly extracted from stem or buds). Certain other 80 species that were identified as toxic due to their high content in pharmacologic active compounds (which could have harmful, even lethal effects on animals and human, if they are accidentally consumed) are used strictly controlled in veterinary and human medicine as natural drugs or traditional botanical preparations.

Currently harvested parts of the medicinal plants are leaves, flowers and the whole plant (herba), but also fruits, roots, seeds bark and buds. Graphic 1 show which is the plants' part usually crafted in Romania from the wild flora.



Graphic1. Currently harvested parts of the medicinal plants

Different criteria, such as botanic, chemical, geographical as well as industrial interest for plant manufacturing, could be used to classify the medicinal plants and to define the specificity of these valuable local bio-resources.

7.1.2. Botanical aspects

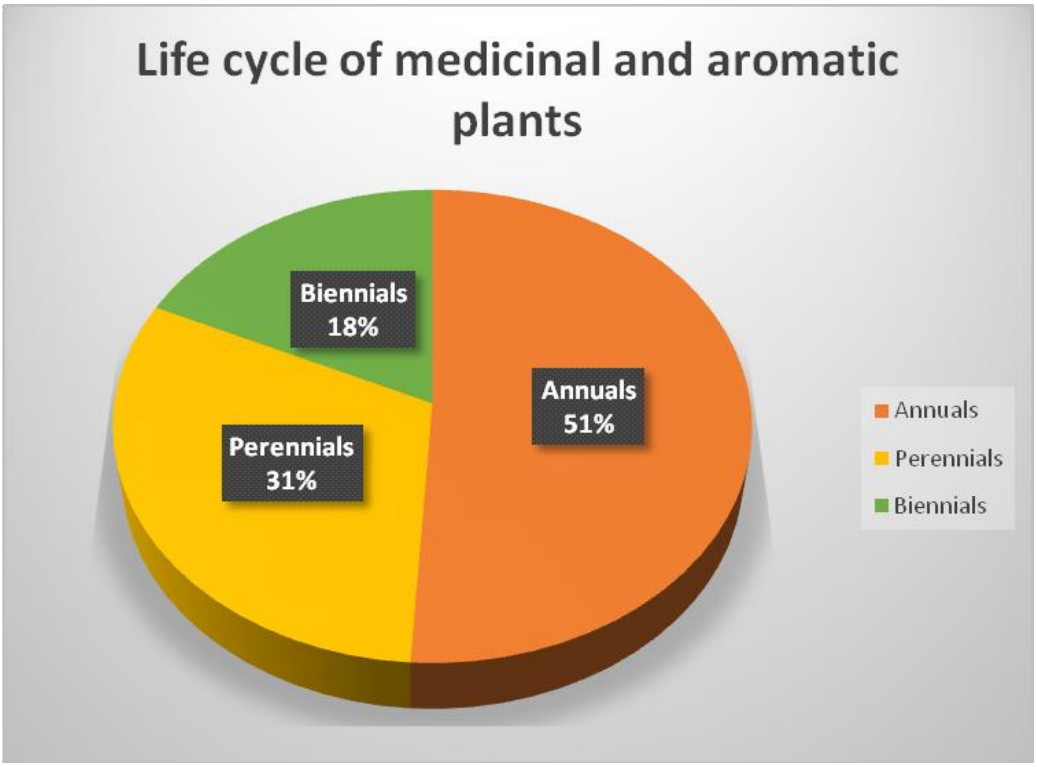
Systematic point of view, medicinal species belong to different families, but there are concentrated in two Monocots families and nine Dicots families which contain dozen genera and over hundred species/each, as it could be seen in Table 1.

Table 1. Plant families containing over 100 species with therapeutic value

Family	Genera	Species
I. Monocots		
Liliaceae	45	165
Orchideaceae	45	135
II. Dicots		
Asteraceae	89	331
Fabaceae	91	313
Ranunculaceae	31	208
Lamiaceae	46	189
Rosaceae	28	146
Apiaceae	34	123
Rubiaceae	35	118
Euphorbiacaee	30	104
Asclepiadaceae	29	101

Most of the medicinal species that could be found frequent in Romanian spontaneous flora belong to the *Asteraceae*, *Lamiaceae* and *Rosaceae* families (5-10%), less frequent are found the members of *Ranunaculaceae*, *Fabaceae* and *Aristolochiaceae* families (2-5%), while not at all frequent are the members of the *Poaceae* and *Violaceae* families (less than 2%).

Taking into account the life cycle, quite half of the medicinal plants are annual species, the rest being perennial species and biannual species. Graphic 2 show this distribution in Romania's species.



Graphic 2. Categories of medicinal plants classified by life cycle

As to the life forms, in Romania there are: 36.4% hemicryptophytes, 20.06% therophytes and 17.9 phanerophytes; the rest of ¼ is composed by geophytes (8.64%), hemitherophytes (7.01%), chamaephytaes (4.32%), hydro-helophytes (1.54%), hydrophytes (1.54%), chamaephytaes-hemicryptophytes (1.23%), hemicryptophytes - hemitherophytes (0.30%) and epiphytae (0.30%).

7.1.3. Ecologic aspects

The variety of soil, climate and relief resulted in a rich plant biodiversity in many regions of the world, which is subject for protection and rational use during last years, especially in developed countries.

Ecologic plasticity of medicinal plants makes these species able to grow under less favorable climatic conditions due to their capacity for secondary metabolite synthesis and accumulation in different parts/organs of the plants (Mathe, 2000). They are resistant to different stress such as hot and drought, diseases and pests attacks, but they also have a significant capacity of soil phyto-remediation.

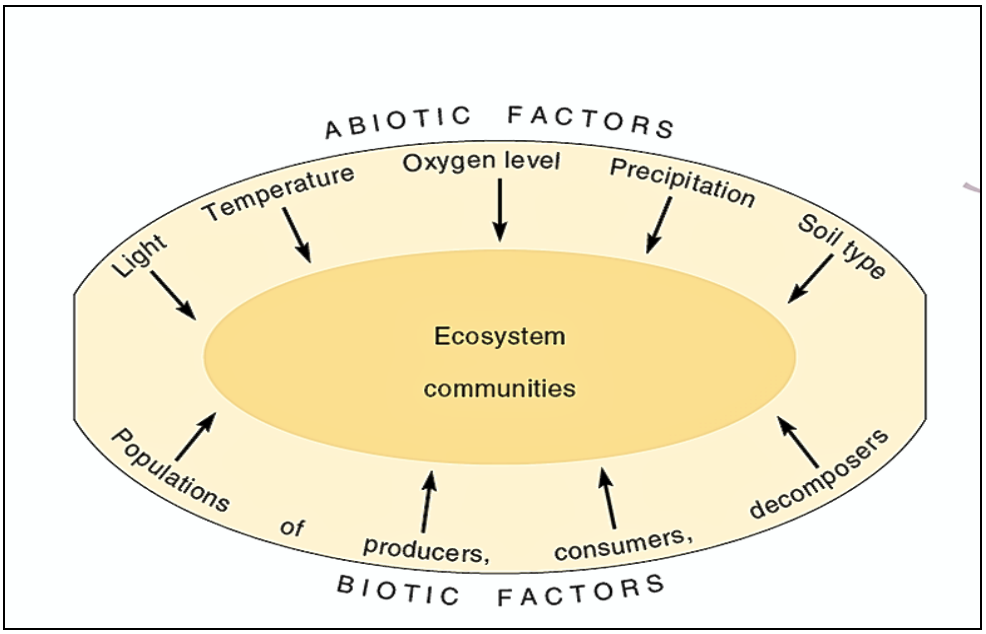


Figure. 1. Importance of biotic and abiotic factors for ecosystem communities

Metabolites are end-products of cellular regulatory processes and they should be regarded as the ultimate response of biological systems to genetic or environmental changes (Figure 1).

The set of metabolites synthesized by a biological system constitute its „metabolome". As the synthesis and accumulation of secondary products is a process connected to plant development and its growth, all differentiation points may induce qualitative new growth processes that can be reflected (directly or indirectly) in the synthesis of secondary products. Thus, the influence of ecological factors may change the chemo syndrome notions; owing to the large number of processes involved in chemism and to the variability in the interrelationships between these processes, the study of any system of chemical characteristics must be performed through the both intermediate and end products.

For the plant, the biological role of secondary metabolites is very important. The essential oils, for example, due to their complex chemical profile, physical properties and volatile substances (flavour profile), they are able to protect plants from heat or cold, to attract or repel insects, to defend against harmful microorganisms (bacteria, fungi), to deter mammals or insects that would otherwise eat them. Essential oils may also mimic insects' pheromone, fooling a male (to attract pollinators, for example) or induce neurotoxic effects to specific insects, acting as a genuine pesticide.

For the human beings, herbs' biochemical compounds are very important due to their nutritional value and physiological effects. Thus, different species with similar bioactive compounds were discovered and used for similar purposes in different countries, while a single plant could be used in

more natural remedies due to different categories of bioactive compounds isolated by specific methods. A relevant example is camomile, which is efficient as anti-inflammatory (due to chamazulene and matricine from the essential oil) and has also antispasmodic effect, due to the polyphenolic compounds, respectively.

Some examples of bioactive compounds found in different plant species and their physiological effect are shown in Table 2.

Table 2. The main bioactive compounds from medicinal species and their physiological effects

Bioactive compound	**Plant species**	**Physiological effects**
Essential oils	*Chamomilla; Pimpinella; Carum; Foeniculum*	Carminative, cholagogue, galactogog
	Ocimum; Cynnamom	Indigestion, loss of appetite
	Juniperus; *Lavandula*; *Melissa; Mentha*	Antispasmodic, antiseptic, choleretic
Sesquiterpene lactone	*Achillea; Tanacetum*	Anti-migraine, anti-inflammatory, cytotoxic, antimicrobial
	Valeriana	Sedative, antispasmodic
	Calendula	Antispasmodic, healing
	Ginkgo biloba	Improving circulation and cognition
Alkaloids	*Aconitum* sp. (aconitine, mesaconitine, hypaconitine)	Pain relief; traditional used in stroke and heart failure, diarrhea, diabets
	Chelidonium	Gall bladder disease, liver disease
	Atropa	Antispasmodic
	Datura; Leonurus; Papaver; Thea	Stimulant, diuretic
	Vinca	Cerebral/brain circulation
Glycosides (cardio-tonics; anthraquinones; iridoids; tioglycosides)	*Digitalis; Adonis-*	Cardiotonic
	Lamium; Nerium; Prunus; Rhamnus	Laxative, purgative
	Brassica	Revulsive, antirheumatic
Coumarin, furano-coumarin	*Ammi*	Photosensitizer (vitiligo)
	Melilotus	Anti-inflammatory-anticoagulant
Flavonoids, flavonolignans, polyphenols	*Silybum*	Regenerating and hepatoprotector
	Cynara	Hepatic metabolism
	Vitex	Hormonal dysfunction
	Ononis; Passiflora; Phytolacca; Polygonum; Populus; Ribes-	Capilaroprotector; hypotensive

Hydroxy derivatives anthracene	*Rheum; Senna/Cassia; Aloe-*	Laxative
Saponins, mucilage	*Malva; Linum; Plantago; Pulmonaria*	Emollient
	Glycyrrhiza; *Primula*	Expectorant
Tonic bitter substances, resins	*Angelica; Humulus; Salvia; Gentiana; Taraxacum*	Digestive disorders, flatulence, inflammation of the intestinal mucosa
Tannins	*Juglans; Vaccinium; Querqus; Rubus*; *Potentilla*	Astringent, antidiarrheal
Sulfonic derivatives	*Allium*	management of hypertension and hypercholesterolemia antibacterian
	Raphanus	Antitussive and immunostimulant

7.2. Traditional use of medicinal plants

Plants and their secondary metabolites have a long history of use in modern 'western' medicine and in certain systems of traditional medicine, and are sources of important drugs such as: atropine, codeine, digoxin, morphine, quinine and vincristine.

In some cases, the active principles of plant-derived products have been isolated and characterized, and their mechanisms of action are understood (e.g., ephedrine alkaloids in some species of *Ephedra*). For many other species, however, including virtually all of the most common products in the marketplace, such information is incomplete or unavailable.

This is in large part due to the complexity of herbal and botanical preparations; they are not pure compounds. It is also a function of the traditionally-held belief that the synergistic combination of several active principles in some herbal preparations is responsible for their beneficial effects (IARC Monograph).

The past decades (starting with the latter half of the twentieth century) have obviously witnessed a tremendous surge in acceptance and public interest in natural therapies both in developing and developed countries, with these herbal remedies being available not only in drug stores, but now also in food stores and supermarkets (Dikinson and MacKay, 2014). This resurgence of interest in herbal medicines was particularly observed in Europe and North America, where herbal products have been incorporated into so-called "alternative", "complementary", 'holistic" or "integrative" medical system.

On the other hand, during the latter part of the twentieth century, increasing interest in self-care resulted in an enormous growth of popularity of traditional healing modalities, including the use of

herbal remedies. Consumers have positive attitude towards these products, because they believe in their natural origin, they trust such products are more likely to be safe than the drugs. Natural products became part of a healthy lifestyle because people think they can help to avoid the unnecessary contact with synthetic drugs and conventional medicine.

It is estimated that up to four billion people (representing 80% of the world's population) living in the developing world rely on herbal medicine products as a primary source of healthcare and traditional medical practice, where the use of herbs is viewed as an integral part of the culture in those communities (Bandaranayake, 2006). Traditional Chinese medicine, for example, is still common in use in China. Botanical products are used only after some kind of processing (stir-frying; soaking in vinegar or wine) and more than half the population regularly use traditional remedies. They account for approximately 1/5 one fifth of the entire Chinese pharmaceutical market (Li, 2000).

Monographs on selected herbs are available from a number of sources, including the European Scientific Cooperative on Phytotherapy (ESCOP), German Commission E and the World Health Organization (WHO). The WHO monographs, for example, describe the herb itself by a number of criteria (including synonyms and vernacular names) and the herb part commonly used, its geographical distribution, tests used to identify and characterize the herb (including macroscopic and microscopic examination and purity testing), the active compounds (when known), dosage forms and dosing, medicinal uses, pharmacology, contra-indications and adverse reactions.

7.2.1. Traditional botanical preparations

Traditional botanical preparations offer some guarantees of efficacy and safety (after such a long history of use and data on different types of population) as well as numerous available information (dosages, pharmacological, toxicological activity of natural substances) and physiological impact on human health.

Actually diverse "natural products" known for health benefits (herbal teas, tinctures, syrups, aromatic vinegars, creams) were easy to be prepared using different parts (fresh or dried) of medicinal plants, fruits or seeds which could be pressed for juice or oil extraction, boiled, macerated or vapour distillate.

Different extraction techniques of the bioactive compounds have as result a large range of preparations:

- aqueous extracts, such as infusion (flower; leaf, herba), decoction (root, seed), maceration (cold water for mucilage);
- hydro-alcoholic extracts (tinctures, alcoholate or alcoholature), which have certain advantages (such as extraction of both lipophilic and hydrophilic constituent, improved efficacy);
- products obtained by maceration: oil (cold and hot), vinegar, honey;
- distillation products (essential oils obtained from stem or flowers);
- natural exudates (oleoresin or gum-resins obtained by incision in the bark of conifers).

The extraction parameters, namely the duration of maceration and extraction, temperature adapted, plant/solvent ratio are very specific. It has also to be mentioned the importance of the type of preparations and of the dosages, because they may have certain consequences. *Teucrium chamedrys* is a relevant example: aqueous extraction ensures no toxicity, while in dry powder there were identified some insoluble chlordane diterpenes that can induce severe cytolytic hepatitis (risk of hepatotoxicity).

Some recommendation and practical advices focus on the most appropriate combination of plant species (targeting synergic or complementary effects), limitation of the number of basic plants (no reason to exceed 8-10 plants or botanical extracts in one product) or plant extracts supporting the taste (no more than 3-5 extracts in one product). When not respecting these rules there would be difficult to identify chemically the final product; to understand the interactions of all the substances present in the final product; to face with unknown composition of mixtures and potential toxic compounds (Anton et al., 2012).

The progress in knowledge regarding botanical preparations were registered in the fields of isolation, concentration, purification of pharmacologically active compounds by using chemical solvent to obtain: titrated extracts (adjusted at a special level of a *well known active constituents* with an inert ingredient or with a mixture of extracts); quantified extracts (standardized with a well *defined level of markers in* mixing some batches) and purified extracts (process used in order to increase the concentrations until to obtain a pure chemical substance).

While the researchers focused in the past on complex formulation («theriaca»: a saturation of all physiological receptors), today it is of interest the concentration of active constituents in plant extracts and tomorrow will be the isolation of pure active compounds without any « ballast » (Anton *et al*., 2012).

7.3. Sustainable use of natural resources

Taking into account the long history of medicinal plants use and wild-crafted, the quality of raw material and the interest in certain valuable medicinal species, as well as the trend of global demand for exploitation of natural resources (which is expected to increase between 10 to 16% per annum (GOI, 2000), it seems that the destructive and inappropriate harvesting techniques could lead to extinction of many species, menacing livelihoods in the long run.

7.3.1. Biodiversity conservation

The WHO/TUCN/WWE International Consultation on Conservation of Medicinal Plants (held in Chiang Mai, 1988) was followed by several other declarations and sets of recommendations calling for the *in vitro* and *in situ* conservation of threatened species, cultivation, for sustainable production and wild crafting of medicinal plants (Fig. 2).

The new approach regarding the environment policy has as the main target to develop new paradigms to build a green future in which biological resources from farmland, sea and forest can be sustainable converted into food, feedstuffs, biobased products and energy with minimal loss or waste.

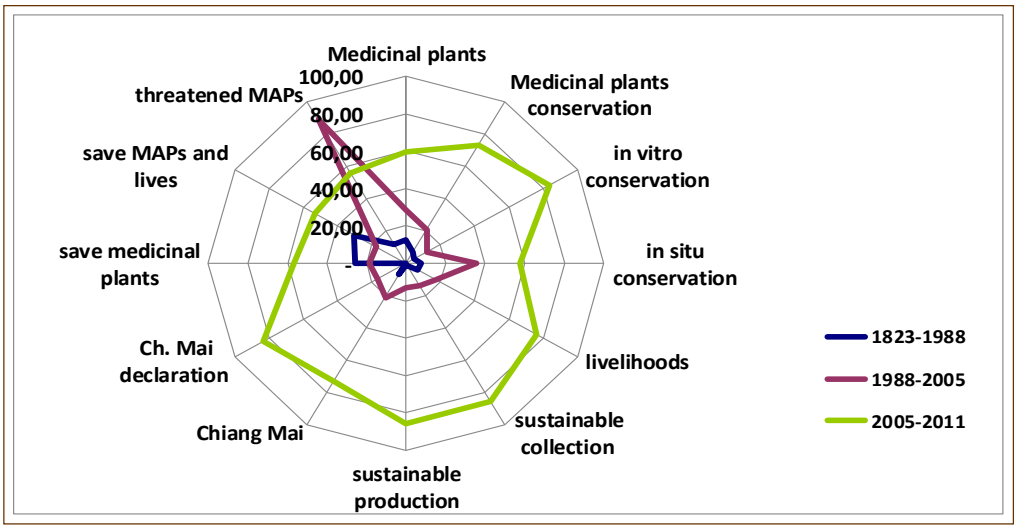


Fig. 2. Evolution of the areas of interest in herbs protection (1823-2011) (Mathe, 2016)

In Romania, the old activity of wild-crafting has usually supported the family needs (especially in villages and small rural communities) but reached the industrial scale at the beginning of the XX century, when it was developed a real network of medicinal plant manufacturing companies (PLAFAR TRUST). In the years of ’80s, Romania had got its best performance in the field of wild-

crafting, when it was able to export in twenty countries medicinal plants as raw material for different industries (Stoianov, 2003).

But the sustainable use of local resources (63 species mainly crafted from wild flora in 2000 year) asked for the biodiversity conservation. A practical solution was to domesticate and introduce into cultivation the endangered species (e.g. *Angelica archangelica, Gentiana lutea, Arnica montana*) for which were registered increasing demands.

Today 297 species are *ex situ* persevered, 179 species are hold by Suceava Gene bank and 13 species, are on the National Red List (under the severe control of Romanian Academy of Science - Committee for the Nature Monument Protection).

In the Romanian National Catalogue of Plant Genetic Resources (published with the support of the IPGRI), the medicinal and aromatic plants covered a whole fascicule (Murariu *et al*., 2002).

7.3.2. Cultivation versus gathering

First data about cultivation of medicinal plants are linked to the monasteries that were organized as hospitals. The monks had developed "medicinal gardens" and patients' diseases were treated by using local manufactured products based on herbs, minimally processed.

The increasing of industrial needs (certain medicinal species, parts of the plants or some bioactive compounds only) was correlated to agriculture development, because the modern industry prefers to use standardized extracts as active botanical ingredient for herbal drug, cosmetic or food supplement formulations. Controlled and traceable production and processing is already an internationally recognized necessity.

Nearly 10% of raw material comes now from cultivated source that offers the buyers more consistent quality and a lower risk of adulteration than do their wild counterparts.

The first cooperatives (named "ADONIS', "CHAMOMILLA" and "DIGITALIS"), specialized in certain herbs species cultivation were organized in Romania since 1925. Due to the favourable climatic conditions, medicinal plants were cultivated year by year on larger areas (up to maximum 39,000 ha in 1990), when Romania produced near 20,000 tones/year of dry weight material: 30% leaves, approximately 16% flowers, 15% herbal, 13% fruits, 11% roots, less than 5% seeds, 2.5% bark and 2% buds.

The Romanian scientists have studied 95 species of cultivated medicinal and aromatic plants (Mocanu, 1999). The eco-physiological needs of the cultivated species were established, the most

appropriate region for each species was defined and the map of geographic distribution of medicinal plants was set up.

More than 20 technologies of cultivation (about 80 technological sequences) have been established, focusing on: cropping, soil preparation, fertilization, methods of plant multiplication, sowing period, amount of seeds/ha, sowing depth, raw intervals, maintenance requirements, pest prevention and cure, management and control of parasites, harvesting methods, plant drying and storage conditions, processing techniques for fresh and dry raw material, etc.

The main cultivated species were: *Coriandrum sativum, Sinapis alba, Brassica nigra, Foeniculum vulgare, Cynara scolymus, Hyssopus officinalis, Silybum marianum, Papaver somniferum, Digitalis lanata, Datura innoxia, Mentha piperita, Mentha crispa, Salvia officinalis, Calendula officinalis, Melissa officinalis.*

As a result of the experience accumulated in selection and breeding activity, there have been homologated 29 new cultivars of 17 medicinal species.

Medicinal plants growers, raw material suppliers for herbal products as well as food business operators have to implement good manufacture practices along the whole food chain. It could be noticed a real multiplicity of guidelines regarding herb species not only in Europe, but also in USA, China and India, countries with long tradition of use of medicinal plants and huge markets of „natural products". Some of the most useful are:

- ✓ WHO guidelines on good agricultural and collection practices (GACP)
- ✓ EUROPAM - European Herbs Growers Association (Batch Certification)
- ✓ HMPC Guideline on GACP - European Medicines Agency
- ✓ Good Agricultural and Collection Practice - American Herbal Products Association
- ✓ Indian Council on Agricultural Research
- ✓ China - Guidelines for Good Agricultural Practice (GAP) of Medicinal Plants and Animals

7.3.3. Good manufacture practices

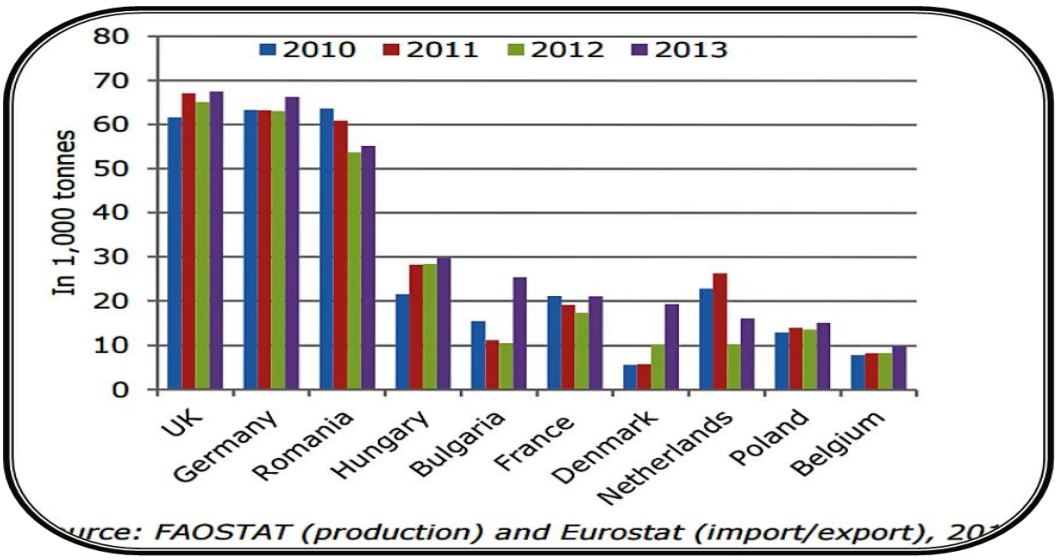
The market pressure due to the higher demands for natural products, the people trust in 'green pharmacy' and herbal medicines associated with the research progress in the service of quality assurance have influenced the development of plant manufacture sector, which proved to be flexible and quickly adapted to the customer needs.

While small and medium enterprises had implemented new technologies and European standards of Quality Management System (ISO 9001/2000), adopted HACCP principles (food industry) and

GMP (for plant processing), the big pharmaceutical companies diversified their production, invested in marketing and advertising, developed new business partnerships and create own networks of distribution. Thus the whole sector followed the global trends, starting to create also organic production, to sustain the market research and to understand the consumers' behaviour.

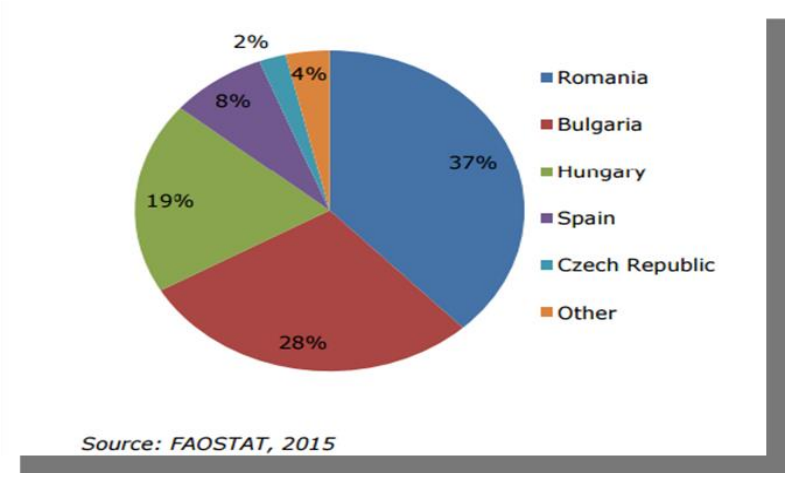
7.4. Trends in herbs production and consumption

Graphic 3 show the dynamic of some EU Member States production of herbs during the period 2010-2013. It could be noticed a group of three countries (UK, Germany and Romania) which have quite double, even triple volumes of medicinal and aromatic plants (production and import-export) as compared to all the others. While in 2013 it was observed a significant increase in Bulgaria and Denmark, for most of the countries the level of production and import-export was quite constant during the period 2010-2013, with a very slow trend of increase in UK, Germany, Hungary and Poland.



Graphic 3. Some EU Member States production, import and export of herbs during the period 2010-2013.

Statistical data for the same period, regarding the consumption of herbs, showed that three eastern countries (Romania, Bulgaria and Hungary) had a very high consumption of spices and herbs. It could be seen in Graphic 4 that these countries are covering together more than 2/3 of the whole consumption from the period 2010-2013.



Graphic 4. Consumption of spices and herbs by EU member states (2010-2013 period)

7.4.1. Safety of medicinal plants: a precondition for use

Both spices and medicinal plants have to ensure high quality and efficacy as a precondition to safe use. Many hazards associated to air pollution, water and soil contamination were identified both in wild-crafted and cultivated species (Figure 3).

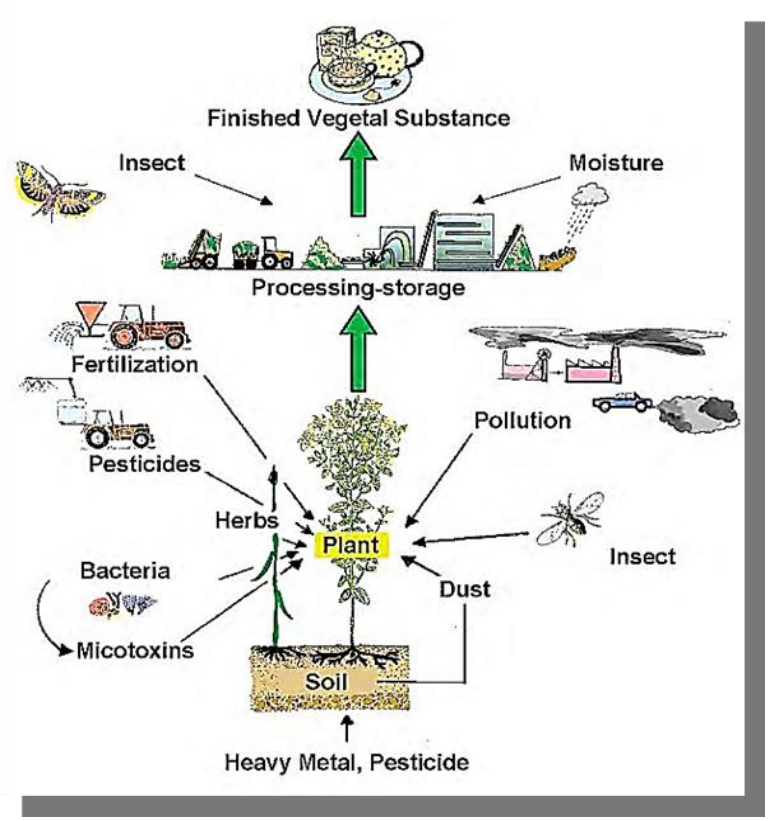


Figure 3. The main safety risks associated to medicinal plants
(After: Novak and Iguera, 2015)

The management and control of all these specific safety risks is very important for:

- processing industry (plants used as raw material; final "natural products" put on the market);
- environment quality (pesticides; radiological hazards; drug residues; products of decomposition; pests and parasites);
- consumers health (allergenic materials; limited levels of natural flavouring agents; unapproved food colours and other additives).

On the other hand, the scientific and regulatory bodies from EU and USA focused on the botanicals specific issues, and had as results some important documents, for example: EFSA Compendium of Botanicals, guidelines for good manufacture practices, public lists of alert substances or new bioactive compounds for which was scientifically proved a reason of worry, BELFRIT list of plant species that should be safety used in herbal food supplements, etc. Further initiatives are needed to achieve the desired harmonization in the mutual recognition of inter-operable compatible multitude of standards between EU member states.

7.4.2. Progress in research and development

There is a continuous need to ensure the quality of medicinal plant products by using modern sample preparation and control techniques, as well as suitable standards. As a result new and sophisticated analytical methods have been developed. They have the advantage to be used in the subsequent chains of quality assurance to guarantee reliable plant sources and good quality of final products.

European projects, co-financed in the 7th EU Framework Program such as PlantLIBRA aimed to foster the safe use of food supplements containing plants or botanical preparations, by increasing science-based decision-making by regulators and food chain operators. This collaborative project involved 25 partners from 14 countries (Spain and Romania between them) belonging to 4 continents and put together universities, public research institutes, small and medium–size enterprises, industry and non-profit organizations having as main objective to establish the levels of intake, benefit and risk assessment of herbal food supplements consumption.

The strong need of small companies for innovation, training and knowledge transfer in food quality and safety field is also a good opportunity for research-development sector to run oriented projects, organize training courses, support new qualification, etc. In this respect, the on-going Program HORIZON 2020 is a new chalenge for "innovative ideas based on cutting-edge research".

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