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Chapter 16

From Medicinal Plant Raw Material to Herbal Remedies

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Additional information is available at the end of the chapter

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Abstract

The use of medicinal plants is old as the existence of mankind. According to World Health Organization (WHO) data, about 80% of world population are using products based on medicinal herbs. Phytotherapy is based on the use of herbal drugs and medicinal products for the purpose of prevention and treatment. Rational phytotherapy is a modern concept of herbal medicines using, which are made of standardized herbal extracts. The quality of each final product is guaranteed by the use of raw materials of a standard quality, defined process of production, and validated equipment. Quality control of herbal drugs and herbal isolates (tinctures, extracts, and essential oils) is done according to the requirements of Pharmacopoeia and other relevant regulations. The scope of phytopreparation quality control depends on its pharmaceutical form. The formulation of a new phytopreparation is a process that has strictly defined phases: from analysis of literature and market, through defining recipes, validation of the production process, quality control of a final product to the preparation of technological and registration documents. The aim of this chapter is to present the process of herbal preparations production from selecting plant raw materials to herbal remedies (on the examples of making tea, tea mixture, drops, gels, and capsules).

Keywords: medicinal plants, medicinal plant raw material, quality control, formulation of phytopreparation, regulations

1. Introduction

Since ancient times, medical plants and simpler herbal remedies have been used in all parts of the world for the treatment and alleviation of various ailments. Although the use of medicinal plants is as old as mankind itself, their controlled application, the isolation and characterization of active substances, started only in the early nineteenth century. It is a known fact that

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the extractive plant isolates and isolated active substances played a major role in the development of modern pharmacotherapy. Many of the isolated compounds are still used today, or they have served as a model for the synthesis of a large number of drugs [1].

The use of plants as medicines has a long history in the treatment of various diseases. Plants especially those with ethnopharmacological uses have been the primary sources of medicine for early drug discovery.

Herbal remedies, from simple to complex forms, should be made of the raw materials required for quality, because only then they could be safe and effective for use. The Pharmacopoeia monographs, Monographs European Medicinal Evaluation Agency (EMEA), which encompasses monographs World Health Organization (WHO), European Scientific Cooperative on Phythotherapy (ESCOP), and Commission E (The German Commission E is a scientific advisory board of the "Bundesinstitut für Arzneimittel und Medizinprodukte" formed in 1978. The commission gives scientific expertise for the approval of substances and products previously used in traditional, folk, and herbal medicine) national regulations, precisely defined parameters of control quality.

The process of drafting a new herbal remedies is very complex and strictly defined phase. Each step in the process is important, from the initial idea, market analysis, selecting high-quality plant material and ancillary pharmaceutical raw materials, recipe formulation, production preparation, quality control of product, preparation of documentation, protection of intellectual property rights, to the introduction of herbal drug in regular production. The drafting process must be validated and secure documentation.

In modern pharmacotherapy, despite the widespread use of drugs obtained by chemical synthesis, the importance of herbal medicines in the treatment and prophylaxis is still large. According to the latest WHO researches, 11% of the 252 basic medicines are in fact herbal preparations [1].

2. Development and manufacturing of herbal preparations

2.1. Use of medicinal plants through history

The use of medicinal plants in the prevention and treatment of various diseases is known since ancient times. Documents of exquisite value show that herbs were extensively used by human population throughout the history. Since ancient times, people have sought safety and relief for their health problems in medicines from nature. Prehistoric men have dared to use particular medicinal plants, based on careful observation of the behavior of animals who have been using them [2, 3]. Over time, the use of herbal medicines and other natural products has developed on the basis of both positive and negative experiences. The collected rich experiences have gradually developed into folk medicine, such as traditional European medicine, traditional Chinese medicine, Indian Ayurveda, Japanese Kampo, or traditional Arabic and Islamic medicine. They consist, not only of herbal remedies but also of other types of drugs, for example, from minerals or animals, or physical procedures [3].

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Material evidence on the use of medicinal plants in the distant past is kept by many ethnographic and archaeological sources. The oldest of these sources are clay tables, discovered in Mesopotamia (2600 BC), which in addition to the description showed also therapeutic application and galenical form in which the plants were to be used. In those ancient times, medical plants mentioned were castor oil, grapes, coffee, oils of cedar and cypress, licorice, myrrh, and poppy juice [4, 5]. The ancient Egyptian papyrus, Ebers Papyrus (1550 BC), represented some kind of first Pharmacopoeia. Egyptians were known for their skill of embalming, distilling scented water, and making perfume of aromatic plants, and for those they were using many medicinal plants that are still in use today (aloe, peppermint, plantain, poppy seeds, and coriander) [6]. The first written records about the use of medical herbs in Chinese traditional medicine date from the third millennium BC. Emperor Shen Nung made a collection of wild medicinal plants. He is credited with the discovery of tea and many of which are used nowadays: cinnamon, ephedra, rhubarb, camphor, and great yellow gentian [6, 7]. The Indian holy books provide many examples of the treatments using medical plants, widespread in that country. A large number of aromatic herbs and spices that are still in use nowadays throughout the world, such as pepper, cloves, nutmeg, originate from India. According to data from the Bible and the holy Jewish book, the Talmud, during various rituals accompanying a treatment, aromatic plants were utilized such as myrtle and incense [7].

With comprehensive development of science in ancient Greece, the pharmacy also receives a special place. The most famous doctor of ancient Greece, which is considered to be the "father of medicine," is Hippocrates (460–377 BC). He was the first to systematize overall medical and pharmaceutical experience and publish them in the capital work Corpus Hyppocraticum. The most ancient botanist Theophrastus (371–286 BC) together with his students founded the first botanical garden in Athens. He described more than 500 most important medicinal plants. Among others, he referred to cinnamon, iris rhizome, false hellebore, mint, pomegranate, cardamom, fragrant hellebore, monkshood, and so on. In the description of the plant, its toxic action was also stated [4, 7]. The founder of the European pharmacognosy, a Roman doctor of Greek origin, Dioscorides, who lived in the first century BC., described medicinal plants which were used in the ancient world, in his capital work De Materia Medica. Dioscorides' most appreciated domestic plants were as follows: willow, camomile, garlic, onion, marsh mallow, ivy, nettle, sage, common centaury, coriander, parsley, sea onion, and false hellebore. The strong influence of Hippocrates and Dioscorides was notable in the school of Alexandria, where some of the major breakthroughs in medicine were made. Unfortunately, a great fire has destroyed the vast library with approximately two million books, and at the same time all the knowledge of medicinal plants of that era [4, 7]. By the Roman conquest of Greece, Romans took over all the medical and pharmaceutical knowledge and certainly the most important mind in this area was the Roman statesman and military leader Pliny, the Elder (23–79). He is the writer of the capital work Historia naturalis. The most famous Roman doctor and a pharmacist is well-known Galenius-Galen, who lived from 131 to 201 and is considered to be the father of galenic pharmacy. In his writings on the development of complex preparations or galenic preparations, he described 304 drugs of plant origin [4].

The Arabs preserved a large amount of the Greco-Roman knowledge during the Dark and Middle ages (i.e., fifth to twelfth centuries), and complemented it with their own medicinal

expertise, and with herbs from Chinese and Indian traditional medicines [8]. The treatments during the Middle Ages were conducted in the restricted environment of monasteries. Skills of cultivation and collection of herbal medicines, as well as making simple herbal remedies, were reserved for doctors-monks. They used the different herbs: mint, sage, tansy, anise, fenugreek, savory, and so on [7].

At the time of Charles V, the famous medical school of Salerno was founded and started its rise by introducing and applying experiences of Arab medicine and pharmacy. Benedictine monks played an important role in the preservation of the Greco-Roman tradition. Their legacy was large botanical gardens where mainly medicinal plants were grown [4]. The Arab world has promoted many sciences including medicine and pharmacy. Certainly, the most famous Arabic doctor was Abu Ali Ibn Sina (Avicenna) and his famous book, The Canon of Medical Science, has been translated into Latin and other languages, and has been used in Europe for many years.

In medieval Europe, the level of medical knowledge was quite low. Arab medicine, starting from the twelfth century, began to penetrate into Europe, through Spain and Sicily. The Arabic books were translated into Latin medicine, and in this sense also the Arabic translations of ancient Greek and Roman books. Paracelsus (during the late Middle Ages) argued that the salubrity of plant originates from chemical compounds that are represented in it [4]. In the eighteenth century, Swedish botanist Carl von Linné (1707–1778) created the Latin nomenclature for each plant (the name of the genus and species), and a botanical system for determining the species, which due to its transparency and convenience is used even nowadays. Scientific pharmacy began only after the French Revolution, and with it the development of the science of medicinal plants. In this area, the most distinguished pharmacists became Lavoisier in France, Scheele in Sweden, Priestley in England, and so on. [4]. The turning point in the approach and the use of herbal medicines is considered to be the beginning of the nineteenth century, when a German pharmacist Sertürner managed to isolate the alkaloid of morphine in its pure form, from poppy (1806). In the period from 1817 to 1820, French scientists isolated a whole series of alkaloids: caffeine, emetine, quinine, cinchonine, and strychnine. Improvements of instrumental analytical methods have allowed further detection of other groups and complexes of active substances, such as heterosides, saponosides, tannins, vitamins, and so on [7].

In the twentieth century, a large number of synthetic drugs were created and it represented the beginning of commercial production of a large number of allopathic medicines, which significantly led to neglect the use of herbs in pharmacotherapy.

2.2. Plants are valuable sources of drug discovery

As already mentioned, herbal medicines have been an extremely important source for the discovery of many drugs. Morphine, which was the first purely natural product to be isolated, was introduced in pharmacotherapy in 1826 (Merck). The first semisynthetic pure substance of aspirin, salicylic acid-based, was isolated from the bark of *Salix alba* willow and was produced in 1899 (Bayer). This was followed by the isolation of active compounds from old herbal drugs, such as digitoxin, codeine, pilocarpine, quinine, and many others, some of which are still in use today. Many herbal remedies, emerged after extensive scientific tests of

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"old and well-known" medicinal plants, were introduced in the therapy. Silymarin, extracted from the seeds of *Silibum marianum*, is used as a hepatoprotective, Paclitaxel from the bark of *Taxus brevifolia* in the treatment of lung, ovarian, and breast cancer, and Artemisinin from *Artemisia annua* herb to combat multiple-resistant malaria [1].

In recent years, many herbal medicines have found their way into the official medicine. Some of them are Dronabinol and Cannabidiol isolated from *Cannabis sativa*, Tiotropium derivative of atropine from *Atropa belladonna* for combating obstructive and chronic bronchitis, Galantamine, alkaloid from *Galanthus nivalis* which is used to relieve symptoms of Alzheimer's disease, and Apomorphine, which is a semisynthetic compound based on morphine from *Papaver somniferum* and is intended for people suffering from Parkinson's disease [1]. We can certainly say that a large number of medicinal plants, which in the past, were used and represent an important raw material for the production of herbal medicines, or have served as a model for similar synthesis of new molecules.

Given that man is an integral part of nature, the human body is compatible with medicines coming from nature. Nature, much like a flawless, perfect complex of laboratories, has created a variety of sophisticated active compounds contained in herbal medicines, which have a huge range of remedial action. Perhaps, this fact will speed up serious research of old manuscripts related to herbal medicines and brings out the "old drugs" of pure historical curiosity [8].

2.3. Basic terms related to herbal medicines

Phytotherapy, as a complementary part of pharmacotherapy, has an important place in many areas of modern medicine. It represents a system of treatments based on the use of natural medicinal resources (drugs) and herbal remedies (herbal remedies) in the purposes of prevention and treatment.

Herbal drug is the whole or grained, dried part of a plant, algae, fungi, or lichen, which is used for its medicinal properties. In addition to the plant organs (above-ground part of the blooming plant as flower, leaf, root, bark, fruit, and seed), plant exudates can also be considered as a drug (resins, balsams, and rubber). Herbal medicines, herbal remedies, or herbal medicinal products (HMPs) contain as active ingredients exclusively herbal drugs or herbal drug preparations. Herbal drug preparations are obtained from drugs, with the procedures of distillation, extraction, filtration, and so on. This concept does not include powdered forms of drugs, essential oils, fatty oils, tinctures, and extracts [9, 10].

Rational phytotherapy is a modern concept of use of herbal medicines, which was designed in Germany at the end of the last century and soon widely accepted in other European countries. It was created from the need to improve phytotherapy, in order for herbal preparations to be more efficient, safer, and their use based on the results of clinical trials. Herbal medicines, which are used in rational phytotherapy, are prepared from standardized herbal extracts, the chemical nature of their active principles is known, they exhibit dose-dependent therapeutic effect, their adverse effects and contraindications are known, and their pharmaceutical quality is well defined and standardized [11, 12].

Herbal medicines are used preventively, in the treatment of milder forms of a disease, or as adjunctive therapy for the treatment of chronic diseases. Most commonly, they are applied with the dysfunction of the respiratory, digestive, urogenital tract, mild, and medium forms of anxiety and depression, as well as of different lesions of the skin and mucous membranes. Their healing effects accrue gradually, so that the maximum effect manifested 2–3 weeks after the application.

2.4. Regulations

According to the WHO, preparations based on medicinal herbs are used by 80% of the world population. Medical use of medicinal plants has a long tradition in Europe, while in some parts of the world (e.g., China and India), herbal remedies still represent a central link in the chain of health services [13].

Extractive isolates of herbal medicines and herbal preparations are extremely complex multicomponent mixtures, as opposed to synthetic drugs that are most commonly a single pure compound. In the production of herbal remedies, certain actions and procedures are needed to be undertaken (collecting medicinal plants from spontaneous flora and plantation cultivation, obtaining extractive isolates, and their characterization), which do not precede the production of synthetic drugs. Fortunately, the procedures of making herbal medicines are largely modernized and defined in all segments. There are a number of guidelines that prescribe standards in all aspects of making herbal medicines: The European Medicines Agency guidelines for the quality of herbal medicines, the WHO guidelines provide standards and guidelines for good agricultural practices, good laboratory practices, and so on. The development of new, sophisticated analytical, and technological methods and procedures within the development and characterization of extractive isolate has greatly improved the quality of the final plant products. On the other hand, the process of harmonization of the quality system for the production and herbal drugs control is present in many countries. But globally speaking, more effort is yet to be made in order to revive the prescribed guidelines and regulations in practice [3]. The main goal of the Committee for herbal products (Herbal Medicinal Product Committee—HPMC) is to prepare a detailed list of monographs and processed herbal substances and preparations, which are in medical use for long enough time that their use is safe under normal conditions. The monograph contains the professional opinion of the Committee on a particular plant products based on scientific data or traditional use within the European Union (EU). For each plant, the substances are stated indications, speed, usage, and other relevant data concerning its safe use or composition that contains it. List and versions of monographs are available for public consultation [14]. In Europe, companies can apply for three different types of market authorization of an herbal medicinal products (HMPs):

- Full implementation. Manufacturer of a herbal drug must provide documentation proving its efficiency and safety, and studies are identical to those submitted for the registration of a synthetic drug.
- Well-established use. Manufacturer of a herbal drug may be permitted to register, on the basis of the submitted detailed scientific literature, stating that the herbal medicinal preparation

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is in use for medical purposes not less than 10 years in Europe and has recognized efficiency and an acceptable level of safety.

- Traditional use. Efficiency and safety of a herbal drug can be accepted on the basis of long experience. Herbal remedies can be registered, if the documents prove their use in mitigating certain ailments, not less than 30 years, with at least 15 years in Europe.

The registration procedure for herbal medicines, at all levels of the European Union (EU), is done according to European Directive 2004/24/EC, which introduces simplified, but strictly defined procedures and affects the harmonization of existing national legislative regulations. Regarding the registration in the non-EU countries, despite the efforts made within the framework of national legislation and harmonization in larger systems, a limited number of herbal medicines have been registered. Therefore, the identification of problems and discrepancies and the systematic plan for overcoming them represent a major challenge for the presence of these herbal drugs on the market of EU countries [15].

In Republic of Serbia, legislation on plant products is harmonized with recommendations of The European Directive 2004/24/EC. Law on medicines and medical devices (Official Gazette of the Republic of Serbia No. 30/2010), Regulation on health safety of dietary products (Official Gazette of RS No. 45/2010), Guidelines of Good Manufacturing Practice, Annex 7- Manufacture of herbal medicines, are all in effect. According to the Law on medicines and medical devices, Herbal medicine, is each drug whose active ingredients are exclusively one or more substances of vegetable origin or one or more herbal preparations, or one or more substances of vegetable origin in combination with one or more herbal preparations. Traditional herbal medicine may be based on scientific principles and is the result of tradition or other traditional therapeutic approaches. The active components of a herbal medicine/traditional herbal medicine are herbal drugs and herbal preparations and their combinations, and this is widely accepted in all European and national documents. In the context of food supplements (dietary supplements), a new the Regulation defines the notion of herbal dietary supplements. These are supplements that contain medicinal plants, their parts or preparations and their quantity in a daily dose of the product should not be less than 15% and greater than 65% compared to a known therapeutic dose of these plant materials or preparations.

2.5. Parameters of quality and quality control

The quality of each final product is ensured by the standard quality of raw materials, the application of validated production processes and procedures on validated equipment. It is similar with herbal remedies, which are made of high-quality herbal raw materials, extractive preparations (extracts and tinctures) and isolates (essential oil and fatty oil). The latest European Pharmacopoeia Ph Eur 8 comprises 270 Monographs on herbal drugs and herbal drug preparations [16]. Monographs define parameters of quality control.

2.5.1. Quality control of herbal drugs

The basis of high-quality herbal remedies is the plant material of a standard quality. Many factors affect the quality of plant material. Regardless of whether the medicinal plants are grown or collected from the wild, biogenetic factors are certainly important (species, variety,

chemotype, and sorta). The following are the conditions in which a plant grows as air, climate, land, then agro-technical measures that are applied during the large-scale production (proper sowing, irrigation, fertilization, control against weed and pests), and then collection from the wild or harvest of the plantation, transport, proper storage, drying, and grinding. It is very important to educate people how to deal with the collection of herbal raw materials from spontaneous flora, as well as those who grow the plants, whether they are doing so in the conventional conditions or organic conditions of medicinal plants production. Quality control of herbal raw materials is strictly defined and traceable. First, the identification of plant raw materials is approached. Responsible and expert persons in laboratories for the pharmaceutical control or in other relevant institutions, conduct identification, and categorization under a certain number.

Table 1 gives a list of parameters of quality control of herbal drugs by Ph Eur 8.0, based on whose defined border values the quality of herbal drugs can be determined. For all the aforementioned

Parameters of quality control	
Herbal drugs	1. Definition: the name of the herbal drugs and content of active substances 2. Characters: appearance, taste, odor, solubility 3. Identification: macroscopic and microscopic examination, TLC 4. Tests: water, loss on drying, total ash, foreign matter, insoluble matter, extractable matter, swelling index, microbiological purity, bitterness value, broken drug 5. Assay: essential oils, tannins, declared active substances (GC, LC, UV-VIS)
Herbal drug preparations	**Dry extract (*Extractum siccum*)** 1. Definition: standardized dry extract prepared from..., content of active substances 2. Production: method of extraction and solvents 3. Characters: appearance 4. Identification: TLC 5. Tests: loss on drying, total ash, microbiological purity 6. Assay: declared active substances (LC) **Liquid extract (*Extractum fluidum*)** 1. Definition: liquid extract produced from …, and content of active substances 2. Production: method of extraction and solvents 3. Characters: appearance, taste, odor 4. Identification: TLC 5. Tests: ethanol, methanol and 2-propanol, loss on drying, microbiological purity 6. Assay: declared active substances (LC, UV-VIS) **Tincture (*Tinctura*)** 1. Definition: tincture produced from…, and content of active substances 2. Production: method of extraction and solvents 3. Characters: appearance, taste, odor 4. Identification: TLC 5. Tests: ethanol, methanol and 2-propanol, dry residue, microbiological purity 6. Assay: declared active substances (LC, UV-VIS) **Essential oil (*Aetheroleum*)** 1. Definition: essential oil obtained by …, and content of dominant components 2. Production: method of extraction and solvents 3. Characters: appearance, odor, solubility 4. Identification: TLC and chromatographic profile (GC and GC-MS) 5. Tests: relative density, refractive index, optical rotation, chromatographic profile

Table 1. Parameters of quality control of herbal drugs and herbal drug preparations (Ph Eur 8).

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parameters, Pharmacopoeia prescribes the procedure. Any organization deals with herbs, forming his specs-attests that rely on the requirements of the applicable European Pharmacopoeia, standards, national regulations, and internal regulations. Definition includes biological source of drug, the Latin name of the genus and species, and the minimum amount of essential oil in the case of aromatic drugs or the minimum quantities of active substances to which the drug is declared. Characteristics define appearance, odor, taste, and solubility. Identification in addition to macroscopic analysis (organoleptic inspection), which includes appearance, color, odor, and microscopic analysis, is carried out for certain herbal drugs, followed by chemical analysis (specific chemical reactions and thin-layer chromatography (TLC)). Predicted tests include water, loss on drying, total ash, foreign matter, swelling index, microbiological purity, bitterness value, starch, and broken drug. Assay includes essential oils, tannins, declared active substance (gas chromatography (GC), GC/mass spectrometry (GC/MS), liquid chromatography (LC), and UV-VIS spectroscopy). For the evaluation of herbal raw materials quality, in addition to the determination of microbiological safety, complete analysis of the health safety is often performed, according to the current regulations (which includes not only the results of physical, physicochemical, and chemical tests but also organoleptic findings, preservatives, sweeteners, mycotoxins, metals and metalloids, pesticide residue, microbiological tests, and radioactivity).

2.5.2. Quality and quality control of extracts

The extracts are one of the most widely used herbal preparations. The extracts can be liquid, semi-solid, or solid consistency. They are most commonly made of dried and grained plant material. For the extract production various processes may be applied: maceration, percolation, extraction of the continuous, and so on. Nowadays, the procedure for extracting plant material by super critical fluids is increasingly in use [17–20]. Tinctures are extractive products which are usually obtained by the method of maceration.

The most often used extragents are ethanol, water, mixtures of water, and ethanol. The choice of solvent depends on the nature of ingredients that need to pass into the extract. In the product declaration, the ratio of components of the solvent mixture used for extraction must always be given. The quality of obtained extract depends on the plant material, the solvent, the drug/solvent ratio, and the extraction process technology. The process of extracts standardization is common. After the quantitative analysis, the extract is adjusted in order to contain a particular amount of an active compound or the group of compounds (or a marker compound) using an inert material or another extract [21]. Parameters of quality control of extracts are shown in **Table 1**. Qualitative and quantitative analyses of the essential oils are carried out by methods GC and GC-MS according to regulation Ph Eur or modified method [22].

2.5.3. Quality and quality control of phytopreparations

When it comes to *mono-components teas,* their quality matches the one defined for the individual drugs (**Table 2**). Quality control refers to the verification of the identity, the declared weight of packaging, and microbiological safety. In the case of *multi-component (mixtures) teas,* their control refers to the verification of the identity of each herbal drug on the recipe, checking the declared weight relationship of the components and microbiological purity.

Phytopreparations	Parameters of quality control
Mono-component tea and tea mixture	1. Identification 2. Appearance 3. Verification of components, declared mass ratio of components 4. Verification of package weight 5. microbiological purity
Liquid herbal preparations (liquid extracts, tinctures, and mixtures of extracts or tinctures), **herbal drops, solutions, syrups**	1. Identification 2. Appearance 3. Loss on drying 4. Content of ethanol 5. Relative density 6. Refractive index 7. Verification of package weight 8. Qualitative and quantitative analysis 9. microbiological safety and/or complete health safety control
Semi-solid forms (herbal gels, cream, and unguent)	1. Identification 2. Appearance 3. Verification of package weight 4. pH value 5. microbiological safety and/or complete health safety control
Solid-dosage forms (capsules, tablets, etc.)	1. Identification 2. Appearance 3. Declared mass of single-dose preparations 4. Disintegration 5. Qualitative and quantitative analysis of the declared active components 6. microbiological safety and/or complete health safety control

Table 2. Parameters of quality control of phytopreparation.

When a herbal remedy represents a *mixture of plant extracts or tinctures*, it is usually difficult to perform the quantitative analysis of active ingredients for each individual extract. For these preparations, the content analysis of active substances for which the preparation is declared is conducted (LC, UV-VIS spectroscopy, GC and GC-MS spectrometry, infrared (IR), nuclear magnetic resonance (NMR), etc.). Also, in principal, a manufacturer appends the typical fingerprint of chromatogram, spectrum, or some other physical parameter, of the preparation ingredient, which may be used by a control laboratory for identification. This approach can also be used for the quantitative analysis of the preparation.

Semi-solid forms (herbal gel, cream, and ointment) are checked for authentication, filling, pH, and microbiological purity. For *solid-dosage galenic forms* (capsules, tablets, etc.), a control is performed for each individual dose. Control for these forms of herbal remedies includes authentication, appearance, the declared weight of the package, or of the each individual dose of the preparation. Qualitative and quantitative analyses of the declared active components, or a marker compound, of the preparation, are obligatory. For this analysis, similar (or appropriately modified) methods to the analysis of herbal drugs or extractive preparations are applied (if not according to Pharmacopoeia, these methods must be validated by the CPMP/ICH/281/95)s.

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2.5.4. Monitoring of phytopreparation stability

Medicinal herbs and products based on medicinal herbs are very sensitive to external influences—the presence of elevated temperatures, moisture, and direct light. They are prone to reactions of oxidation, degradation, hydrolysis, and evaporation, so during the preparation of herbal remedies special attention must be placed to a number of factors that can affect the quality of the final product. In order to determine the stability of a product, to define storage conditions, and durability, stability tests are carried out, which include the investigation of the environmental factors effect on the change in the final product quality. Stability tests are performed at different stages of development and production. During the period of investigation, the first stress test is carried out, in order to select the most optimal, compatible excipients, and the best formulation. All raw materials used, excipients, active ingredients, and extraction products, are subject to stability testing and durability defining, for appropriate packaging and under certain environmental conditions. Stability is defined as the period during which the product remains within the set quality limits of the prescribed specification. In accordance with the requirements of the EMEA, various specific stability tests are placed for different herbal [23].

2.6. Planning and development of new herbal preparation

The formulation of a new herbal products is a process that has strictly defined phases and includes the work of several sectors of the company that is developing products based on medicinal herbs. The dynamics of the process is divided into stages, and they are completed by performing a multitude of necessary activities. Of course, the scope of new product development depends on the complexity of the galenic form of the new herbal preparation. All steps are defined in the documents of quality standards and other regulations of the company (**Figure 1**).

Furthermore, the procedures of developing a new herbal preparation will be explained on the example of the development of herbal remedies in the Institute for Medicinal Plant Research "Dr Josif Pancic," Belgrade, Republic of Serbia (the Institute).

Stages in the development of new herbal products have their logical sequence. Administration, management, the sales department, and the demand of patients expressed through visits to our herbal pharmacies may suggest the need for a new preparation, to the department of pharmaceutical research and development. Management gives the order to the department of pharmaceutical research and development, to create a team that will be allocated to the project and appoint a project manager.

Project manager, who is usually a doctor of pharmaceutical sciences in the field of pharmacognosy, forms a team, writes, and presents a plan for a new product development. The plan, according to the system of quality management, must contain general information: project name, the subject of research, description of development activities, the aim of the research, the necessary equipment, an indication of the place of realization of activities, project duration, and start time of the applicability of the project results. The second segment is represented through dynamic activities (through phases) and the engagement of researchers

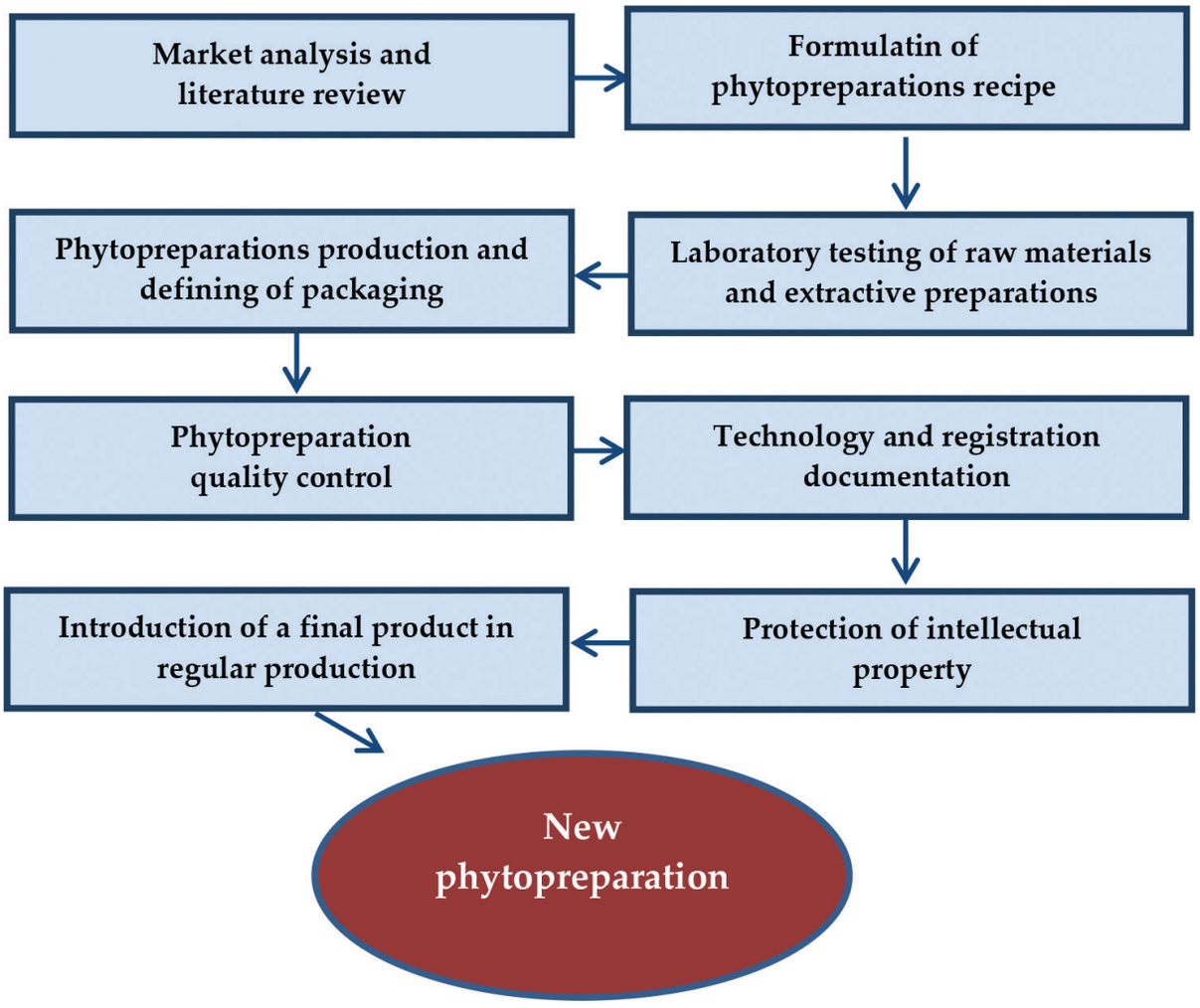


Figure 1. Schematic representation of the planning and development of new herbal preparation.

(throughout activities phases). The third segment is the planning of all material costs for the development of a new herbal remedy. When management of the Institute approves the presented plan for developing a new product, project manager starts with its execution.

The beginning phase represents preformulation studies. Market analysis and the review of relevant literature are very complex. It covers the activities of the Institution's herbal pharmacies that collect patients' requirements, commercial department, which collects data on herbal remedies from the observed therapeutic groups in the domestic and foreign markets. Analysis of relevant literature includes search for relevant directives and monographs, scientific, technical papers, patents, and so on.

When all relevant data are collected, an expert research team approaches the formulation of a recipe. The recipe for herbal remedies and the content of active substances, which will be declared in the preparation, depends on the plan for a herbal product registration. In addition to the selection of galenical form, auxiliary materials are also selected at this stage. Of course, the recipe is subject to small corrections during the production process.

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Further on, laboratories are included in the process of preparations formulation. Analysis of active substances in the selected plant raw materials and quality control prescribed by Pharmacopoeia or other relevant document are performed. Then, the quality control of semi-final product is conducted. In the case of capsules, the analysis of the active substance in dry extract is performed, and also the analysis of other parameters that define its quality, and that is defined by Pharmacopoeia monographs or summarized in an internal specification or a certificate.

Afterwards, the preparation formulation is conducted (formulation of teas or herbal drops, herbal creams, capsules, etc.). In addition to the main plant raw materials, secondary raw materials are selected, which will synergistically facilitate the functioning of the dominant plant drugs, and auxiliary pharmaceutical raw materials are selected. Auxiliary raw materials are used as the basis for semi-solid galenic forms (creams, ointments, and gels), and capsule fillers (for the preparation of granules—mass for the capsule filling).

When the herbal remedy is designed, all laboratory examinations are carried out, as prescribed in specifications. The determination of the average capsule weight is performed, also the determination of active ingredients per capsule, stability testing for active substances per capsule, the capsule dissolution testing, and testing of complete health safety.

From the Intellectual Property Office, the search "recharge" is required and then the protection of the preparation name. The proposal for the primary and secondary packaging graphic layout is carried out. Technological documentation gets completed (processes specifications, recipes, and norms). After the test production of capsules, the production of capsules is introduced into regular production. The validation of technological processes, the validation of equipment, and the validation of laboratory methods are performed. Registration documentation, report writing, and the presentation of results are being prepared.

When the preparation is produced and packed in its primary and secondary packaging, quality testing of the final product is conducted (tea blends and herbal drops, ointments, and capsules). Quality testing is conducted according to the attest or the specification of the final product. It is necessary to examine the complete health safety of the preparation. The stability of the active substance is also monitored, to determine and define the expiration date.

Along with a new preparation production, the writing of technical documentation that represents the preparation file is carried out. The specifications of raw materials, semi-final products, and auxiliary materials are written. In order to define the dose for preparations, it is necessary to determine the range of content of the active substance. This is achieved by validation of the process, on the validated equipment.

Finally, the registration documents are prepared. The scope of the documentation is correlated with the desired herbal remedies group for registration (herbal medicine, traditional herbal medicine, or dietary supplement). If it is planned to register a new product as a herbal medicine or a traditional herbal medicine, then the instructions of the EMEA monographs need to be followed. If it is planned to register a new product as a dietary supplement, then the dose needs to be below 65% of the therapeutic dose.

Development of different galenic form of herbal remedies is presented in the following examples.

2.6.1. Mono-component tea

Herb yarrow *Achillea millefolium* L. is highly regarded medicinal and aromatic plant and has a long traditional use. According to WHO monograph, yarrow exhibits antibacterial, anti-convulsant, anti-inflammatory, antioxidant, antipyretic, antispasmodic, and antiviral activity. According to the Commission E monograph and the EMEA, yarrow is traditionally used only for temporary loss of appetite, mild spasmodic complaints of the digestive organs, bloating, flatulence, and externally as a bath with problems in the lower abdomen in women, and with superficial wounds [24].

The process of making mono-component tea from yarrow takes place in the following stages:

- Purchase of high-quality herbal material (overground top part of the blooming herb), which meets the quality parameters as prescribed by Pharmacopoeia.
- Grinding the herb up to a prescribed degree of fragmentation. Grinded herbal drug as a semi-final product is controlled on the microbiological safety, which is performed in accordance with the relevant regulations for tea and Pharmacopoeia requirements.
- Following the positive results obtained from the pharmaceutical and microbiological laboratories, chopped herbal drug is placed in packaging.
- Final product, mono-component yarrow tea, is sent for the control to pharmaceutical and microbiological laboratories. Pharmaceutical laboratory confirms the authentication and filling volume.
- When a controlled product receives the confirmation that corresponds to the standard quality, it is dispatched to the warehouse of final products and further distributed to pharmacies and other places.

The user manual is adapted to the prescribed use as a traditional herbal medicinal: as a means of relieving complaints of the digestive system, improve appetite, eliminate gases, regulating the secretion of bile, pains and cramps in the stomach, with the amenorrhea.

2.6.2. Tea for weight loss in filter bags (1.5 g)

For this indication, herbal drugs that have diuretic and laxative effect have been selected on one hand, and on the other hand, we have drugs that aid digestion and herbal drugs rich in polyphenols as potent antioxidants and vitamin C. The following herbal drugs are included in equal parts (ana partes) in the mixture composition: *Betulae folium, Frangulae cortex, Foeniculi fructus, Thea folium,* and *Cynosbati fructus*. The mixture of herbs whose active ingredients regulate digestion and excretion of urine, stimulate metabolism, and facilitate the breakdown of fat, and thus contribute to the cleansing and detoxification of body. Its is recommended as a supplement in weight loss diets and for helping to reduce and maintain a desired weight.

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The process of making tea for weight loss in filter bags is as follows:

- Purchase of high-quality individual herbal material and quality control of parameters as prescribed by Pharmacopoeia.
- Grinding the herb up to a prescribed degree of fragmentation. Grinded herbal drugs are controlled on the microbiological safety and Pharmacopoeia requirements (appearance, moisture content, content of essential oils, impurities, and degree of fragmentation).
- Following the positive results obtained from the pharmaceutical and microbiological laboratories, homogeneous mixing of grinded herbal drugs is carried out, and then in the machine for tea bags, bags are filled with the contents. Afterwards, they are placed in special filter bags and packaging.
- Final product, herbal mixture in filter bags, is sent for the control to pharmaceutical and microbiological laboratories. Pharmaceutical laboratory confirms the authentication and filling volume of tea bags and the number of tea bags in a packaging.
- When a controlled product receives the confirmation that corresponds to the standard quality, it is dispatched to the warehouse of final products and further distributed to pharmacies and other places.

2.6.3. Herbal drops for weight loss

Herbal drops, meant to regulate body weight, represent a combination of tinctures and herbal extracts, whose active ingredients stimulate the metabolism, have a beneficial impact on digestion, and eliminate the excess fluids from the body. The composition of herbal drops includes *Betulae tinctura, Frangulae tinctura, Foeniculi tinctura* and *Cynosbati extractum fluidum*.

The process of making herbal drops at the Institute, takes place as follows:

- Purchase of high-quality individual herbal material and quality control of parameters as prescribed by Pharmacopoeia.
- Grinding the herb up to a prescribed degree of fragmentation. Grinded herbal drugs are controlled on the microbiological safety and pharmacopoeia requirements.
- Following the positive results obtained from the laboratories, homogeneous mixing tinctures and extract, filtered, and then filled into glass bottles.
- Final product is sent for the control to pharmaceutical and microbiological laboratories.
- When a controlled product receives the confirmation that corresponds to the standard quality, it is dispatched to the warehouse of final products and further distributed to pharmacies and other places.

2.6.4. Herbal cream with extract of comfrey: Comfrey gel

The root of comfrey *Symphyti radix* represents a very important medicinal herb raw material. According to the Commission E monograph, it is used for blunt injuries. According to EMEA,

the traditional use of herbal preparations, it is used in semi-solid-dosage forms for cutaneous use. Traditional herbal medicinal remedy is also used for the symptomatic treatment of minor sprains and bruises. Gel with 10% propylene glycol extract of comfrey root (*Symphyti Extaractum fluidum* (1: 7)) containing mucus, tannins, saponosides, and allantoin improves epithelialization, drainage, and tissue regeneration. It has a beneficial effect with swellings, hematoma, fractures, sport injuries, and posttraumatic conditions. It should not be applied to open and infected wounds.

The production process of Comfrey gel is performed in the following stages:

- Purchase of high-quality herbal material *Symphyti radix* and quality control of parameters, as prescribed by Pharmacopeia selection of high-quality pharmaceutical raw materials according to the manufacturer attest.
- Grinding of comfrey root and producing the liquid extract with propylene glycol with a method of percolation. The resulting extract is controlled to authentication, relative density, and microbiological safety.
- Liquid extract of comfrey, after the processing procedure is incorporated into the semi-solid base, and then filled into tubes. The final product, herbal gel from the roots of comfrey, is sent to the control to laboratories.
- When a controlled product receives confirmation that corresponds to the standard quality, it is dispatched to the warehouse of final products and further distributed.

2.6.5. Herbal capsules ODOVAL S®, herbal sedative

Herbal product is used for the defense of organism against the effects of daily stress.

Valerian root (*Valerianae radix*) has a long traditional use. It is approved by Commission E to help combat restless states and difficulties falling asleep caused by nervousness. According to EMEA monograph, it has a well-established use as a herbal medicinal remedy for the relief of mild nervous tension and sleep disorders.

Melissa leaf (*Melissae folium*) is a favorite vegetable drug that is used as a mild sedative, carminative, antispasmodic, and aromatic. The EMEA monograph only credits *Melissae folium* with a traditional use: it is considered to be a traditional herbal medicinal remedy for relief of mild symptoms of mental stress and to aid sleep and for symptomatic treatment of mild gastrointestinal. Capsules of this herbal sedative are designed to have the *Valerianae extractum siccum* as a dominant component, with the synergistic effects of *Melissae extractum siccum*.

Odoval S® is a herbal remedy meant for maintaining mental balance. It contains extracts of valerian root and lemon balm leaf, medicinal plants traditionally used for their calming properties. The active ingredients of these extracts have a favorable effect on alleviating anxiety and irritability, facilitate sleep, and establishment of natural sleep patterns. Odoval S® can be used as a valuable help in alleviating various symptoms caused by chronic stress (mental tension and anxiety during the day, irritability, and feelings of worry).

In the Institute , the production process of capsules is carried out in the following stages:

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- Purchase of high-quality herbal raw material of *Valerianae radix* and *Melissae folium* and quality control on parameters, as prescribed by Pharmacopeia.
- Production of dry extracts: *Valerianae extractum siccum* and *Melissae extractum siccum* in the circular extractor, according to the specifications of the process.
- The resulting dry extract is controlled as a semi-final product to authentication, moisture content, and microbiological safety.
- Controlled dry extracts, along with additional pharmaceutical materials, are used to produce granulate (mass for encapsulation). Granulate, as a semi-final product, also goes to the control to pharmaceutical and microbiological laboratories. Pharmacopoeial method is used to determine the content of valeric acid [2].
- Upon obtaining the results of quality control, encapsulation, that is, automatic filling of gelatin capsules with prepared granulate, is conducted. Capsules are forwarded in the glass jars, and then into the boxes.
- The final phytopreparation is sent to the control to laboratories. The following parameters are determined: properties, number of capsules in a package, the average weight of the capsule content, uniformity of mass capsule, identification of valeric acid LC and TLC for lemon balm, disintegration of capsules, and microbiological safety. The product is sent to the analysis of the complete health safety.
- When results confirm the quality according to certificates and specifications, the final product is dispatched to the warehouse of final products and afterwards distributed to pharmacies and other places.

3. Conclusions and perspectives

Natural products discovered so far have played a vital role in improving the human health and have been the drugs of choice despite facing a tough competition from compounds obtained by chemical procedures, due to their safety and efficacy. The most striking feature of natural products in connection to their long-lasting importance in drug discovery is their structural diversity that is still largely untapped [1].

Comprehensive development of science and technology, able to produce high-quality herbal medicines, is greatly improved in recent decades. The acceptance of herbal medicine as a natural and gentle alternative to synthetic drugs is very high in public in developed countries and, from a global perspective, unit sales of herbal medicines is constantly growing. However, we still face many problems in these areas [2].

A comprehensive approach to these problems, the state of the field of medicinal plants and herbal remedies, can be repaired. A better education of people is involved in the collection and cultivation of medicinal plants on the necessity of obtaining plant raw material of high quality. In particular, it should encourage the concept of organic production herbal products. Producers should be required to produce only quality-assured medicines.

Improved harmonization of regulatory classification of herbal preparations in the world would inevitably lead to greater transparency and consistency of the market.

Special attention should be paid to improving knowledge about the benefits of rational phytotherapy, particularly evidence-based phytotherapy, health workers, especially doctors.

The aim of all efforts would be to improve the overall awareness of the possibilities of choice in prevention and treatment and can judge the effectiveness of the use of medicinal herbs and herbal preparations.

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