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Medicinal Plants in the European Pharmacopoeia (**)

The elaboration of the European Pharmacopoeia (Ph. Eur.) is based on a Convention, an international treaty by which contracting parties undertake to take the necessary measures to ensure that the monographs shall become the official standards applicable within their respective countries.

The technical and scientific body concerned with the elaboration of the Ph. Eur. is the European Pharmacopoeia Commission, which:

— determines the general principles applicable to the elaboration of the Ph. Eur.;

— decides upon methods of analysis for that purpose;

— arranges for the preparation of and adopts monographs to be included in the Ph. Eur.;

— recommends to the Public Health Committee, the administrative organ of the Convention, the date of implementation.

The preparation of the monographs is entrusted to experts selected by the Commission for their personal competence, on the proposal of their delegations. At present, there are 16 groups of experts entrusted with the elaboration of monographs, for instance on inorganic substances, synthetic and natural organic substances, antibiotics, sera and vaccines (human and veterinary), radiopharmaceuticals and plastic containers and materials.

Group of Experts No. 13 on pharmacognosy is responsible for vegetable drugs, and its subgroup No. 13H, for fatty oils and related products.

To establish a common Pharmacopoeia, the Commission had to work out a satisfactory way of selecting monographs. At its early sessions in the 1960s, the Commission, which at that time consisted of 8 member countries, decided

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(**) Presented at the International Congress on «Medicinal Plants» (Sansepolcro (AR), 17-19 October - Roma, October 20th 1987), organized by the Accademia Nazionale delle Scienze detta dei XL.

that a monograph which appeared in at least 5 national pharmacopoeias should automatically be elaborated. Monographs which appeared in only 3 or 4 national pharmacopoeias were to be the subject of a vote.

This situation is reflected in the content of the first edition of the European Pharmacopoeia, which consisted of 362 monographs, of which 38 are on vegetable drugs and fatty oils (a little over 10%).

As you are no doubt aware, since the European Pharmacopoeia was set up in 1964, the number of member states has increased considerably. At the present time, seventeen Council of Europe member states, and one non-member state are Contracting Parties of the Convention.

When the first edition came up for general revision, the system for the selection of monographs was modified, so that the following criteria were taken into consideration:

— therapeutic value;
— extent of use;
— safety in connection with toxicological dangers from impurities such as related substances, residues from synthesis and purification or from deterioration on storage;
— problems arising in the method of control.

Since 1980, two exercises concerning the choice of monographs have been carried out taking the above criteria into account. In this context, it should also be mentioned that in accordance with the Commission's Rules of Procedure, proposals for the elaboration of monographs can be made only by:

— the Chairman of the Commission;
— a delegation, or
— a group of experts, through its Chairman.

1980 saw the beginning of the publication of the Second Edition of the Ph. Eur., which is divided into two parts:

— Part. I contains the revised analytical methods, reagents and annexes from the first edition as well as corresponding new texts;

— Part II consists of monographs. With the publication of fascicule 10, the revision of the first edition was completed. To date, the second edition contains 556 monographs, i.e., revised monographs of the first edition and new monographs.

Of these 556 monographs, 44 concern vegetable drugs and 7 fatty oils and similar products. This accounts for about 9% of all the published monographs. If we add the monographs whose elaboration was authorised in the first and second choice of monographs exercise, the monographs on vegetable drugs and fatty oils account for about 7% of the total.

There is thus a definite tendency for the proportion of the monographs on vegetable drugs and fatty oils to diminish.

However, if these figures are compared with those of some national

STARCH AND MUCILAGE

Acacia
Acacia, spray-dried
Agar
Linseed
Psyllium
Starch: Maize
Potato
Rice
Wheat
Tragacanth

ALKALOIDS

Belladonna leaf
Belladonna, prepared
Cinchona bark
Hyoscyamus leaf
Hyoscyamus, prepared
Ipecacuanha root
Ipecacuanha, prepared
Opium
Stramonium leaf
Stramonium, prepared

STEROIDS

Digitalis leaf
Liquorice root
Senega root

MISCELLANEOUS

Gelatin
Gentian root
Rhatany root
Valerian root

ANTHRAQUINONES

Aloe dry extract, standardised
Aloe, Barbados
Aloe, Cape
Cascara
Frangula bark
Rhubarb
Senna leaf
Senna pods, Tinnevelly
Senna pods, Alexandrian

ESSENTIAL OILS

Anise oil
Aniseed
Camomile flower, roman
Cinnamon
Clove
Eucalyptus oil
Fennel
Lemon oil
Matricaria flower
Peppermint leaf
Peppermint oil
Peruvian balsam
Thyme

FATTY OILS AND RELATED PRODUCTS

Almond oil
Arachis oil
Beeswax, white
Beeswax, yellow
Carnauba wax
Castor oil
Cetostearyl alcohol
Cetostearyl alcohol, emulsifying (type A)
Cetostearyl alcohol, emulsifying (type B)
Isopropyl myristate
Olive oil
Sesame oil
Sodium cetostearylsulphate
Wool alcohols
Wool fat
Wool fat, hydrous

pharmacopoeias, a contrary tendency can be noted. For instance, the Swiss Pharmacopoeia contains, in addition to the « European monographs », another 70 monographs; in Austria these number 100 and in the Federal Republic of Germany about 60, without counting the corresponding preparations. A similar trend is also noticeable in France, as may be seen in the *Notes - Pro-pharmacopée*.

These discrepancies are perhaps due to the fact that in many countries the national pharmacopoeia is not only regarded as an "industrial" pharmacopoeia but is also intended for dispensing chemists, perhaps also to the fact that the importance and the development of pharmacognosy as such vary from one place to another, or again the fact that single substances are given preference over complex mixtures whose composition depends on many factors. These considerations may have led delegations to give different weight to the criteria mentioned above for choice of monographs (therapeutic value vs. extent of use).

Elaboration of monographs on vegetable drugs

Pharmacognosy is concerned with the identification and determination of vegetable drugs and their mixtures and preparations. Formerly, magnifying glasses and microscopes were the standard analytical tools used for macroscopic and microscopic identity tests. These identified the "packaging materials" without, however, yielding any useful information on the active ingredients. Since then, there has been a revolutionary development of vegetable drug analysis as a result of steady progress in the analytical field and growing knowledge of the components of vegetable drugs.

Taking all the monographs already described and those still to be prepared, we can classify these into 7 groups, namely:

— 10 monographs on vegetable drugs containing starch or mucilage;
— 9 on drugs containing anthraquinone derivatives;
— 3 on drugs containing steroids;
— 11 on drugs containing alkaloids;
— 13 on essential oils and drugs containing such oils;
— 14 on fatty oils and related products;
— 4 on miscellaneous drugs.

The elaboration of a monograph on a vegetable drug is comparable with that of a chemical substance, being set out as follows:

— Definition;
— Description of a whole drug;
— Identification;
— Tests;
— Assay;
— Storage.

Definition

Generally speaking, it must be established that, in the absence of any other information, the Ph. Eur. describes the whole drug.

The definition describes the organ(s) of the plants used and, where applicable, the active principle(s).

In the case of drugs containing alkaloids, except for cinchona bark, a minimum limit for total alkaloids is required, calculated in terms of a single alkaloid. For solanaceous drugs, this alkaloid is hyoscyamine and for ipecacuanha it is emetine. For such drugs, in addition to the description of the whole drug, a monograph is devoted to a standardised powder ("prepared drug") with a maximum and minimum content within narrow limits.

Similar information is given in the case of drugs containing anthraquinones: minimum content of hydroxyanthracene derivatives, calculated in terms of a typical component of the drug, for instance, sennoside B in senna leaves and pods, aloin in aloe, glucofrangulin in frangula, rhein in rhubarb and cascaroside A in cascara, with the additional requirement that not less than 60% of the hydroxyanthracene derivatives must be cascarosides.

Where essential oils are concerned, when necessary there are requirements for the minimum content of individual components (for instance, determination of citral in the case of lemon oil) or for multi-components (ester, alcohol and ketone content in peppermint oil).

As a rule, in the case of drugs containing essential oils, only requirements concerning minimum content of volatile substances are given. In the case of camomile, however, in addition to this quantitative statement there is also a qualitative statement, namely that the oil obtained must be blue. For thyme, the monograph which is under preparation, in addition to the total oil content, a determination is also made of the thymol content using Emerson's reaction (treatment of phenol with 4-aminoantipyrine in the presence of an oxidising agent).

The tannin content of rhatany root is determined using the traditional hide powder method, in combination with a photometric method.

Description of the whole drug

This section is made up as follows:

— physical characters;
— macroscopic description;
— microscopic description and
— the description of the drug when reduced to a powder (not to be confused with the drug presented in powder form).

This section also contains the traditional features of the former conventional drug analysis, together with "analytical" characteristics such as the stomatal index.

Identification

The identity tests carried out are qualitative ones intended to characterise the active ingredient(s), either as a group reaction or preferably using chromatography. This will be made clear by the following examples:

Solanaceous drugs: Test for alkaloids using Vitali's reaction.

Ipecacuanha: TLC test for emetin and cephaëline. This test is semi-quantitative, as the size of the spots can show whether the root is derived from *C. acuminata* or *C. ipecacuanha*.

Aloe: Colour reaction for aloin and differentiation between Cape and Barbadoes aloes.

Valerian root: Colour reaction for the valepotriates.

Gentian root: TLC test for amarogentin.

Cascara: Colour reaction for *O*- and *C*-glycosides.

Digitalis leaf: Test for cardenolides using Kedde's reaction and test for the 2-deoxy sugars.

Tests

As regards *Tests*, a distinction may be made between the following:

a. chromatographic methods, currently combined with a chromatographic identity test;
b. macroscopic tests;
c. general methods.

The following are examples of these groups of tests.

a. For Frangula the glucofrangulins and for Cascara, the *O*- and *C*-glycosides are identified. For both drugs, there is also a test for other *Rhamnus* species as well as for anthrones, using *p*-nitrosodimethylaniline (with formation of azo-compounds), in order to ascertain whether the drug is fresh or has been stored.

Peppermint leaf and oil: chromatographic identification of menthol, menthone, menthyl acetate and menthofurane, exclusion of carvone or pulegone indicating the absence of *Mentha crispa* and *M. pulegium*. For Senega root, the saponins are identified by chromatography and their contents determined semi-quantitatively.

b. The macroscopic tests are intended for the exclusion or limitation of foreign matter (i.e., matter coming from the same plant but not defined as the drug) or foreign elements (i.e., matter not coming from the source plant). For the first group, for instance, mention could be made of a higher proportion of stem in the case of leaf drugs and for the second group, of the test for *C. auriculata* in *C. senna*.

c. The "general methods" include, for instance, the tests for sulphated ash,

total ash and ash insoluble in hydrochloric acid. These methods may be described as "indicator methods" since it has been shown in the course of time that the sulphate and total ash content of cultivated medicinal plants has risen steadily because of the use of fertilisers; the second test detects unacceptable quantities of sand, which can occur not only in the case of root drugs but also in that of leaf drugs where there has been inappropriate mechanical harvesting.

It should also be mentioned that the monographs on starch, agar, gelatine and tragacanth, i.e., raw materials used for pharmaceutical preparations, contain a test for microbial contamination: a total viable count is carried out and, where necessary, also a test for specified micro-organisms. The legal status of this test is such that it does not have to be made mandatory by a national pharmacopoeia authority. If, however, it is made mandatory, the requirements stated in the relevant monographs in the form of footnotes must be included unchanged.

The section "Tests" also includes a number of tests it would have been better to include among the index determination. This includes the determination of the bitterness index in gentian, the swelling index in mucilaginous drugs and the flow time in tragacanth.

Assay

The purpose of the assay is to provide a reliable determination of the content of active principles or groups of active principles, in a vegetable drug.

As a result of the constant progress in the analytical field, assays are subject to regular changes and improvements. Thus, in the future, the determination of groups of active principles (for instance, of the total alkaloid content) still frequently carried out at present, will tend to be replaced by differentiated determinations of active principles, particularly in the case of mixtures of chemically similar compounds with very different activities.

As regards drugs used for the industrial extraction of their active principles, for instance quinine alkaloids from cinchona bark and digitoxin from digitalis leaf, such differentiated assays are already carried out, since what is important in this case is not the total alkaloid or the total cardenolide content but the accurate determination of the content of the individual specific active principles.

Here are a few more examples of assay methods:

With the exception of cinchona bark, in all other drugs containing alkaloids, the total alkaloid content is determined acidimetrically after the usual separation and purification steps. In the case of cinchona bark, a spectrophotometric method is specified, which allows a separate determination of the alkaloids of the quinine and cinchonine types owing to their different UV absorption spectra.

For opium, for which the assay has still not been finalised, an HPLC method is envisaged.

For all hydroxyanthracene-containing drugs, the determination is based on the same principle, namely, oxydative hydrolysis of the components to hydroxy-anthraquinone-aglycones, and their photometric determination using Galeffi's

method: instead of an alkali hydroxide solution (Bornträger's reaction) a methanolic magnesium acetate solution is used. This makes it possible to obtain reproducible values, as well as test solutions which are not sensitive to light and oxidisation.

For vegetable drugs containing essential oils, the content of volatile substances is determined using a continuous distillation apparatus whereby the essential oils, after determination of the volume obtained, can be separated for further analysis.

The existing determination of glycyrrhizinic acid in liquorice root is an interesting analytical method: after acid hydrolysis of a drug extract, an aliquot portion is subjected to separation by thin-layer chromatography and the area corresponding to glycyrrhetic acid is scraped off. After elution, the determination is carried out spectrophotometrically against a reference solution of glycyrrhizinic acid CRS prepared under the same conditions. There is no doubt that an HPLC method would be more suitable and more economical.

Conclusion

The active principal content and the composition of a mixture of active principals in vegetable drugs depend on many different factors, e.g., climate, nature of the soil, time of harvesting, drying, genetic factors. These are factors which man cannot always influence. Hence it may be wondered whether from the point of view of the safe use of medicinal drugs and the preservation of quality standards it might not be more suitable to describe both the crude drug and a standard preparation, the latter being used for incorporation into the final pharmaceutical preparation. However, this is not sufficient to ensure the safe use of medicinal substances; the problems arising from the contamination of vegetable drugs by heavy metals, herbicides, insecticides and substances added to prevent deterioration during storage, must be dealt with in responsible fashion by the competent authorities.

A Pharmacopoeia lays down requirements for medicinal substances, auxiliary substances, preparations and other articles. It is therefore an instrument for the quality control of medicines in the public health field, aimed at ensuring the proper quality of medicines which reach the consumer. Whatever one thinks of medicinal plants, the fact remains that, if they are used, controls are necessary.