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Quality Requirements of Medicinal Plants (***)

1. INTRODUCTION

Proprietary medicinal products with medicinal plants or preparations of medicinal plants as active ingredients are of great importance in the Federal Republic of Germany. They will be called 'phytopharmaca' in the following text.

About 85,000 phytopharmaca are at present on the market in Germany. Most of them have to be reevaluated till the end of 1989.

In order to work out sensible criteria for the registration, it is necessary to discuss the scientific problems of the quality of medicinal plants. During recent years this scientific knowledge about medicinal plants has been transferred to legal institutions for the registration of phytopharmaca in the Federal Republic of Germany.

Just lately EEC activities have been taken up again to lay down the special properties of medicinal plants and their preparations and of phytopharmaca in EEC rules, in order to harmonize the requirements in all countries of the EEC.

The basis of the quality of phytopharmaca in general is the quality of the medicinal plants used as starting material. I will concentrate on the question of the quality of fresh and dried medicinal plants in my further argumentation.

2. CHARACTERISTICS OF QUALITY-STANDARD

Reproducible quality of a medicinal product from batch to batch is the basis of a reproducible therapeutic effect. A quality standard must be defined and its specifications must be so clear that this standard quality can be reproduced again and again.

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A monograph in the pharmacopoeia for a special product can be referred to as such a standard. If all its requirements are fulfilled, it is likely that the desired quality is obtained. We will discuss this fact in more detail later on.

In the following step I want to demonstrate which demands exist for medicinal plants and which criteria constitute a reliable standard.

3. Quality-Standard for Medicinal Plants

Before establishing a standard for any medicinal plant, which is oriented to the necessities of a drug, there have to be some general facts and definitions.

3.1 Medicinal Plants as Multi-Component Mixtures

A plant is built up by many compounds, which can be classified in different ways.

When a plant is used as a drug, the following systematical arrangement can be useful:

a) Constituents which determine therapeutic activity (active constituents) such as arbutine, alkaloids or anthraquinones.

b) Constituents which modify the therapeutic action of an active constituent.

c) Constituents without therapeutic or modifying activity.

Unfortunately, this classification is quite theoretical up to now because there are nearly no scientific investigations yet. One cannot point out the active constituents of many of the medicinal plants. This, for example, is the case for such medicinal plants as Matricaria flowers or Valerian roots. Furthermore, only speculations about those compounds of a medicinal plant which modify the therapeutic effect of active constituents can be given.

This ignorance about the function of the different compounds of a plant for the therapeutic effect and the fact that a medicinal plant or medicinal plant preparation is used in its entirety have brought us to regard the whole medicinal plant or its preparation in its entirety as one active ingredient. This is generally valid for all medicinal plants and not dependent on whether active constituents are known or not.

3.2 Chemical Specifications of a Quality Standard

The question comes up as to what it means for the establishment of a quality-standard if the plant is regarded in its entirety as one active ingredient.

The variety of compounds which build up a plant makes it impossible to analyse the identity and quantity of each compound. Therefore only some compounds or groups of compounds are investigated in this way. Thus a quality-
standard which is only based on compounds of a plant always would be very incomplete.

The following compounds are normally determined:

a) Active constituents if known. Their identity and quantity are determined. If a mixture of compounds occurs, it is necessary to determine which single compounds it is composed of, and the relative amount of these compounds has to be investigated as far as possible. The tests have to be designed in a way that chemical races can be identified which differ from the norm in the identity and quantity of the active constituents.

b) Compounds which characterize a certain medicinal plant, without being active constituents, as for example, the flavonoid-mixture of horsetail herb or the sesquiterpene alcohol viridiflorol of peppermint.

c) If these tests are done by chromatographic methods, you will find further mostly unknown substances. These can be used by knowledge of their chromatographic pattern to characterize a certain plant in a better way.

In this manner with the help of their compounds it is possible to establish some kind of a more or less valid quality standard for medicinal plants. We will see later that it is impossible to derive the precise area of the specifications. Plants as living organisms always show a certain variability in their chemical composition, which we have to take into account.

3.3 Botanical Specifications for a Quality-Standard

To compensate for inaccuracies and uncertainties of a quality-standard which is only based on chemical facts, it is necessary to carry out a macroscopic and microscopic analysis as well.

Even though these tests, metaphorically speaking, only investigate the packing-material of therapeutically active substances of a plant, they are necessary in order to prove the botanical identity of a plant or at least to make it probable. The evidence of such investigations is of a lesser effect, if they are carried out with dried and comminuted plant material, in comparison to a fresh plant.

Each of the shown tests by itself only shows little evidence. But the combination of all single results makes it possible to establish a certain quality-standard.

Why the limits of such a quality-standard have to be relatively wide will be discussed now.

3.4 Variability of Medicinal Plants

There are several different facts which influence the composition of a medicinal plant and I will give some examples of how the composition of a medicinal plant can be modified:
a) Plants belonging to a specific species are never genetically uniform. Chemical races are a typical example of this.

b) Even if a uniform genetic structure is given, there are influences in the climate and the environment. These can evoke changes in the physiological behaviour of a plant which can change its compound-pattern.

c) The physiological condition of a plant at the time of harvesting also may influence the chemical pattern of a plant substantially.

If a peppermint plant is harvested quite early during the growth period, the amount of menthol in the essential oil, for example, is fairly high, while if harvested after blooming, the amount of menthofuran may rise dramatically.

d) During the drying process of a plant, unphysiological enzyme reactions may evoke great changes in the compound pattern of a plant. Their kind and amount depend strongly on the drying-conditions.

These and other reasons, not further discussed, make it very difficult to come to a fixed quality-standard for medicinal plants.

3.5 Description of the Quality of Dried Medicinal Plants in a Pharmacopoeia

By taking the reasons just mentioned into consideration, the pharmacopoeia handles the quality-standards for dried medicinal plants quite liberally. This can be understood because of the function of the pharmacopoeia in establishing a framework for quality-standards, which must not be too strict. The required uniformity of the quality for a certain phytopharmacon must be narrower than the pharmacopoeia demands, in order to come to a reproducible therapeutical effect. The pharmacopoeia demands for medicinal plants with known active constituents only a lower limit for these constituents; but especially for active constituents with a high therapeutic activity it is absolutely necessary to specify also the limit of content. This means that it is necessary to establish a certain content range, in order to get a reproducible quality of a phytopharmacon.

3.6 Controlled Cultivation of Medicinal Plants

The best chance to produce plants with a homogeneous and reproducible quality is to cultivate them under controlled conditions. It is to a great extent possible to optimize the seed or plant material, the factors influencing the growth, the time of harvesting and all subsequent working steps. The expression "You cannot test a quality into a medicine" is especially valid here.

3.7 Purity Tests

The purity tests belong to the supervision of quality of medicinal plants by which the safety for therapeutical use can be guaranteed.

The following tests are important:
a) Each medicinal plant is contaminated by microorganisms.

This fungal and microbial contamination has to be limited in numbers. Pathogenic or possibly pathogenic microorganisms have to be absent as well as aflatoxins.

b) In this context one has to realize the practice to reduce microbial contamination by fumigation with several agents, especially ethylene oxide. It is known today that ethylene oxide is cancerogenic. Therefore in the Federal Republic of Germany the fumigation with this substance is strictly limited. It is necessary to apply an assay for the treated material, which has a limit of detection of 1 ppm to make sure that the treated material doesn’t contain any residues of ethylene oxide. The limit of residue of ethylene chlorohydrine as a reaction compound of ethylene oxide was restricted to 150 ppm.

c) Another method to reduce the microbial contamination is by applying ionizing radiation; this method is allowed in Germany since a few months in certain circumstances. The supposition for the use is an admission for using this procedure by the competent national authority. Up to now no application was made and so no reports about any experiments can be given yet.

d) The proof of limits of residue for pesticide contaminations also belongs to the tests of purity. These substances are often used with the cultivation of plants but they may occur with wild growing plants also, if they were grown near treated cultivations. These pesticides are dangerous in two different ways:

— The residue amounts of pesticides at the time of harvesting may be so high that there is a certain risk in the application.

— There are many reports that pesticides may influence the physiology of plants, which may lead to a change of the chemical composition.

— Recently attempts were made to prove residues of some heavy metals like lead, cadmium and mercury which may be harmful to the patient. But no final conclusions regarding these tests and no upper limits of these metals have been set up yet in the Federal Republic of Germany.

— The tests on radioactive impurities are a further problem which came up during the last years. I hope that the degree of this contamination of medicinal plants will decrease again in the future and make tests unnecessary.

3.8 Stability of Dried Medicinal Plants

A medicinal plant normally is used in its dried form. The removing of water is on the one hand necessary for establishing a stable status. On the other hand this removing of water causes great changes with the components, especially during the first step of the drying procedure. By an infraction of cell-membranes which occur during water withdrawal, certain substances may get into contact with certain enzymes, which are normally in different cell-compartments. These uncontrolled reactions will only be stopped or drastically slowed down
when the withdrawal of water has come to a point at which enzymes become inactive. You can make these experiments by walking through a freshly cut meadow. You can smell the changes taking place.

But even in plants with very low percentage of water still some uncontrolled enzyme-mediated reactions may take place.

All these facts show that the drying of medicinal plants and the production of dried plants is a process which may effect substantial alterations of the plant-compounds.

A change of the conditions of drying may result in a different compound-pattern. Besides these enzyme-induced reactions other chemical reactions in the plant can take place, induced by light and temperature.

It is important to keep in mind that even a dried plant is not at all a stable system.

Changes in the compound-pattern normally result in a decreased quality. Investigations of the stability of dried medicinal plants must be concentrated at two points:

a) Which reactions do the active constituents show?

b) Which reactions do the other compounds show?

Both points are of great importance for the quality and the therapeutical effectiveness of a medicinal plant.

The question of the stability of the active constituents can be answered by adequate analysis. The proof of the stability of the accompanying compounds is more difficult. It can be made quite superficially chromatographically by finger-printing analysis. This is why it is hard to make reliable statements about the stability of medicinal plants without known active constituents. It would be wise to respect an advice of our ancestors in this case, namely, to store medicinal plants only until the next harvest. But this may be unrealistic for economic reasons. The only way to solve the problem is to investigate this kind of medicinal plant and to find out about the active constituents, in order to make it possible to prove their stability at least.

A further problem is that several investigations have shown that the stability also depends on the origin of the plant material. Different origins of medicinal plants may show different stabilities. This evidence was given by the investigation of several different samples of fennel fruits.

It is so far unknown whether these difficulties also occur with controlled cultivated plants, but it seems to be quite unlikely.

4. SUMMARY AND OUTLOOK

The quality of fresh and dried medicinal plants depends on several different facts. Therefore it is difficult to establish absolute quality standards which can be observed.
The knowledge of all means of quality changes should enable us to reach a quality which promises or even guarantees a reproducible therapeutical effect. This is the only way to preserve the traditional knowledge of the effectiveness of medicinal plants in a modern technical world which puts such great stress on absolutely reliable quality standards. Only the future will tell whether new technologies as, for example the genetecology, are able to give a new basis for the improvement of the quality of medicinal plants.