Quality management program for Piper methysticum Forst. f.

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Introduction

Since the discovery of Kava (*Piper methysticum Forst. f.*) in the 17th century, the plant has been subject to countless ethnological, biological and pharmacological studies. The major effect consisting in the onset of a sensation of spiritual relaxation within minutes of the intake of the traditional Kava drink, macerations of the roots have been used for social and ritual purposes for centuries in the populations of the South Pacific islands (1). This "instant effect" makes kava roots a very interesting raw material for the preparation of standardized drugs for the European market, where the effects can be used very efficiently in the treatment of stress symptoms and psychovegetative disorders. A quick onset of the relaxing effects after intake of kava capsules or tablets can be ensured by using an adequate method for the preparation of industrial kava extracts, and the optimization of the liberation of the active constituents from the formulation.

The efficacy and quality of natural remedies do not only depend on an appropriate galenical approach, but to a very high degree on the quality of the drug material used in the production process. For drugs originating from uncontrolled sources or wild collections in Third World countries a strict control of the drug quality is hard to maintain. Yet in the past 20 years and still ongoing, a very consistent drug quality concerning the content and composition of the active constituents was achieved for the pharmaceutical preparation Kavasedon®. Lately increasing demands for kava roots by Western consumers resulted in a growing pressure on the limited resources of the producing countries. Although as yet no changes in drug quality could be observed, this situation calls for a closer look at the current situation of Kava in the South Pacific. We therefore initiated a quality management program, addressing several issues:

- Botanical issues: obtaining an overview over the current botanical knowledge on local kava cultivars
- Phytochemical issues: search for potentially relevant phytochemical differences in kava cultivars
- Ethnological issues: comparison of ethnological data on the local use of kava cultivars in the South Pacific with modern pharmacological experience
- Pharmacological issues: testing of the combined influence of the various kavalactones in pharmacological models
- Cultivation issues: evaluation of the possibilities of a systematic kava cultivation in cooperation with local farmers in order to facilitate quality control
- Economic issues: examination of the channels of distribution in place and ecomomic analyses of large-scale cultivation projects.

Most of these issues are still under examination and will be ongoing for the next years. Although by far the slowest step in the research program, the cultivation and ecomomic issue was addressed by one of us (Georges Betti) with good results.

Botanical Issues

Kava is an endemic plant in the islands of Melanesia, Polynesia and Micronesia, having been dispersed from island to island in the course of human migration. According to Lebot et al. (1989, 1991) (2;3) its probable starting point might be the archipelago of Vanuatu in Melanesia.

The sterile shrub *Piper methysticum* is probably the result of constant cloning and vegetative propagation of the wild kava, *Piper wichmanii*, which is abundantly growing in Vanuatu, the Solomon islands and New Guinea. By chromosome counts and isoenzyme analyses, Lebot et al. concluded that *Piper methysticum* was developed starting from Piper wichmanii from Vanuatu, in the first place used for ritual purposes, and later on as a cash crop (1-5).

Figure 1: *Piper methysticum* (left side) and *Piper wichmanii* (right side) from Vanuatu

As a result of centuries of local selection some 120 cultivars of kava are currently known. The differentiation of local kava types by Western standards is mostly difficult, as from the morphological point of view often no distinct differences can be found. Although vernacular names often refer to morphological characteristics, e.g. the length or colour of the internodes, the selection process has always been guided by the physiological effect: only kava types with the desired physiological properties were chosen for cloning by vegetative propagation. The morphological properties are obviously not linked to the content of active constituents respectively their composition. This could by shown by Lebot et al. through extensive comparisons of morphotypes, ethnological usage, and phytochemical analyses of literally hundreds of kava samples throughout the South Pacific (1-5).

Figure 2: Examples of Kava morphotypes from Vanuatu

Nevertheless, local consumers in South Pacific islands clearly distinguish kava cultivars for their physiologic activity – some cultivars are for ceremonial use only, some for medicinal purposes, some for daily consumption, and some kava types are never consumed due to their overly strong or unpleasant effects. For the consumer, kava can be weak or strong, it can be soothing and induce sleep or, on the contrary, it can fail to produce relaxation and can provoke nausea. Drinkers are well aware of these variations and usually want to know which Kava is being prepared or where it comes from (2).

The repartition of kava is limited to a relatively small cultivation area within the South Pacific. Thus, the supplies of kava roots are also limited. With the growing demands for kava root, a deterioration of drug quality might be expected. In that case, a quality management program will have to take into account the differences between kava cultivars.

Phytochemical and ethnological issues

As shown by ample pharmacological evidence, the physiological effects of Kava are mainly based on a small group of kavalactones, i.e. kavain (K), dihydrokavain (DHK), methysticin (M), dihydromethysticin (DHM), yangonin (Y), and desmethoxy-yangonin (DMY). These compounds contribute to approximately 96% of the constituents of kava extracts produced with lipophilic solvents (5).

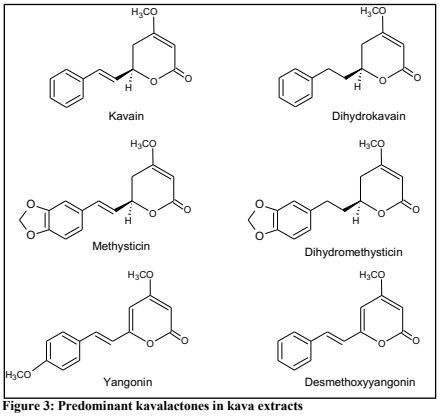

Figure 3: Predominant kavalactones in kava extracts

As early as 1963, within a review on the chemistry and pharmacology of kava, Keller and Klohs stated that there was no systematic examination on the relative potency of extracts produced from different kava types (6). In 1966, Young et al. argued that contradictions in pharmacological observations with kava extracts in animals might have been caused by deviations in the phytochemical composition of the extracts (7). They successfully searched for quantitative variations in kava cultivars with a TLC method. Similar questions were addressed by Duve and Prasad (1981) (8), and by Smith (1983, 1984) (9;10). Due to the differences found between kava cultivars or commercial drugs, in each case the authors claimed the necessity for further botanical and phytochemical studies prior to defining standards.

The studies called for by Keller and Klohs in 1966 were finally initiated by Lebot et al. in the 1980s. By systematic phytochemical observations and cluster analyses regarding the variations in the relative composition of the main kava lactones, more than 100 kava cultivars could be allocated to 6 major groups of chemotypes (2-4). Through extensive cultivation assays, chromosome counts and isoenzyme analyses, Lebot et al. were able to demonstrate that the ratio of the six major kavalactones is genetically determined.

Our quality management project is therefore aimed at the selection of suitable kava types for the optimization of biomass and lactone contents. At the same time, the local preferences for certain kava cultivars shall be correlated to their physiological effects. As the Pacific population looks back on 1500 years of experience, this knowledge – although certainly not consisting of scientific facts – should not be neglected.

Pharmacological issues

In the medicinal literature there is ample evidence for the efficacy of the kavalactones. Yet, we feel that there is still the necessity of examining the biokinetic interactions between the single compounds, as most trials were done either with isolated compounds, or with drug material of unknown origin and composition. The recent discussion of the potential adverse effects of kava clearly shows the gaps in the pharmacological and toxicological interrelations of the active kava constituents.

Cultivation and economic issues

Even though of importance for the local consumption, we could not find any differences in the chemical composition of drug batches exported to European pharmaceutical companies. This might either be explained by regular distribution channels supplying roots from always the same sources, or by average mixtures of different types in the containers en route to Europe. Nevertheless, the question of the discrepancies between the published findings in the kava literature and the observation of a very consistent drug quality remain to be elucidated.

When purchasing kava drug supplies, the exact origin of the roots is mostly unknown to the buyer, the plants themselves being grown in a multitude of locations and islands, sometimes being transported over hundreds of kilometers over the sea to the next collection point. These distribution channels and structures deserve a closer look, as the quality of the drug depends on the observation of certain standards in the collection and drying of the roots. Improvements in the distribution channels would necessarily have to be organized with the local kava growers, who quite often profit the least from the kava trading.

Figure 4: Loading of dried kava roots on small coastal freighters in the main port of Espiritu Santo, Vanuatu

Since Kava was discovered by the OTC market in Europe and the USA, the demands of root supplies are constantly rising. In 1996, Lebot stated exports of more than 100 tons of dried kava roots, with ever increasing demands since then (4). True numbers are hard to obtain, as the local consumption of fresh kava roots cannot be stated, and the islands and even states have a vivid exchange of kava stocks. For example, Hawaii and Fiji are considered to be gross importing states for kava, consuming and trading more kava than the local production can supply.

Most of the kava harvest is collected without defined quality parameters except a minimum content of kavalactones, and without the observation of sustainability or crop management. In spite of local governmental counter-measures such as export restrictions, many islands are already running short of kava due to over-harvesting. Without a strict control, adulterations of drug powder with foreign wood material (8), and even undermixing of roots of *Piper wichmanii* can be seen. Even though *Piper wichmanii* is considered to be the origin and fertile wild form of *Piper methysticum*, and even though the species would meet the specifications set by the kava monographs concerning kavalactone concentrations, *Piper wichmanii* is not used by the native population in the South Pacific if it can be avoided.

A logical solution to such problems would be a project for controlled cultivation within the larger scale of a quality management program. As a matter of fact, this has been tried in the past, so far without success. Kava displays very specific demands in cultivation. The plantation on inadequate terrain such as former sugar cane fields in the lowlands of Fiji, or the large-scale introduction of non-adapted kava cultivars on islands where these new cultivars grew in direct concurrence with local types, resulted in phytosanitary problems and viral contaminations of the crops. In addition, a cultivation project would have to meet the economic standards of European and US American purchasers, in terms of drug pricing as well as long-term supply with a defined drug standard.

One of us (Georges Betti) addressed the cultivation problem in the 1990s in close cooperation with local farmers, using traditional methods of plantation and harvesting, so far with good results. The archipelago of Vanuatu being the origin of approximately 80 kava cultivars (2), the genetic diversity of kava on the islands of Vanuatu was a major reason to place the cultivation experiments there, thus avoiding the necessity of having to introduce new cultivars in a working ecosystem. Already, enough biomass with specified quality parameters for a regular supply of pharmaceutical companies is harvested from the plantations.

Conclusions

The current relationship between supply and demand of kava in the South Pacific calls for a close examination of the quality of the drug material by pharmaceutical companies, and for a more systematic approach in assuring a suitable cultivation and harvesting method in accordance with the needs of the plant and – often neglected – the local population. Such a cultivation program is currently under way in the South Pacific State of Vanuatu, where ideal conditions for an in-depth examination can be found.

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