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THE INDUSTRIAL UTILIZATION OF MEDICINAL PLANTS WITHIN DEVELOPING COUNTRIES

Process Technology Development and Product Standardization*

Background paper

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CONTENTS

1. INTRODUCTION:

WHO has estimated [1] that "perhaps 80 per cent of more than 4000 million inhabitants of the world rely chiefly on traditional medicines for their primary health care needs and it can safely be presumed that a major part of traditional therapy involves the use of plant extracts or their active principles".

It is also recorded [1] that in 1980 the United States alone paid over US$ 8000 million for prescriptions containing active principles obtained from plants. Indeed the total world annual turnover of the industry utilizing medicinal plants has been recently estimated to be of the order of US$ 20,000 million [2]. Obviously, this is exclusive of the traditional usage referred to above, which if included would reflect the staggering impact of plant-derived medicines on human disease therapy. Sustained and systematic industrial interest in exploiting plants for this purpose on a substantial scale has hitherto mostly been confined to countries like China, Korea and India, among developing countries.

Clearly then, if the WHO ideal of Health for All by the year 2000 is even to be remotely approached, developing countries must be helped in their endeavour to mount and sustain multidisciplinary research and development programmes including pilot-scale technology development to industrially utilise the therapeutic potential of their medicinal plants.

Medicinal plants are usually available as an abundant natural resource that could be scientifically used propagated and sustained. The cultivation propagation and harvesting of plants is an industry that has a heavy component of rural involvement. Systematically cultivated plant resources can supply the developing nations with safe, stable, standardized and effective galenical or analogous preparations for primary health care programmes, and the industrialised nations too with new biologically active plant-derived principles that may enter the therapeutic armoury of modern medicine.

These considerat ons have been the framework behind the UNIDO programmes during the past decade, which have sought to accomplish, enhancement of indigenous capabilities in several developing countries for the industrial production of plant-derived pharmaceuticals utlizing the following steps:

- Assessment of natural resource potential and planning the means of utilization.
- Enhancement of indigenous research capability
- Manpower and infrastructure build-up
- Build-up of endogenous technology development capability, at pilot-scale level.
- Introduction of modern techniques of analysis, and quality control methodology.
- Introduction in concept and practice the methodologies of scientific processing and standardization of products.

These considerations manifest themselves in practice in all the major UNIDO programmes now ongoing[3/] e.g. in Burkina Faso, Nepal, Rwanda, Tanzania, Thailand and Turkey and one recently initiated in Vietnam.

2. FACETS OF THE INDUSTRY AND UNIDO'S TECHNICAL ASSISTANCE PROGRAMMES

Some salient features of this very multi-faceted industry need to be described albeit briefly so as to illustrate what has had to be accomplished in initiating the UNIDO programmes mentioned above.

2.1 Collation and Analysis of Information

There is a wealth of information on plants, their therapeutic uses and their chemical constituents. Such information is widely scattered in books, periodicals sundry publications national reports and proceedings of meetings and symposia. Much of this information has recently been collated in modern computerized data-bases which specialize on natural plant products. For developing countries, acquisition of such information is important from several points of view, particularly as research carried out on the same plant species in different climatic and geographical zones can be an indicative guide although they may reveal at times considerable compositional variations. Indeed repetition of such analytical research is often a necessary prerequisite preceding technology development.

An "Indicative List" of plants has been compiled by UNIDO[4/] with the aid of a group of experts listing plant species which are regarded as being of potential industrial value, primarily because it is known that industrially important pharmaceuticals are constituents of these plants.

Similarly, WHO recently published [1/] a list of 119 distinct compounds which are plant-derived, and are currently in use as drugs in one or more countries together with the therapeutic indications associated with these plant-derived drugs.

2.2 Assessment of the indigenous flora, Plant propagation and Management

The assessment of an indigenous natural flora for drug development is briefly called - "Economic Mapping". This constitutes mapping the species in relation of their location/habitat and relative abundance. From this exercise of economic mapping follow plans and programmes for systematic harvesting of the natural flora mindful of considerations of environment and conservation. Methods of plant propagation and cultivation together with crop management would then be the goals of the ensuing research programmes to ensure that adequate supplies of raw material for industrial processing are available.

In this endeavour not only macro-propagation but micro-propagation methods based on tissue culture and methods of genetic improvement of plant species must be considered.

2.3 Research and Development Goals

The programmes of drug development demand multidisciplinary capability. The WHO list of plant-derived drugs indicates clearly that as a result of the scientific follow-up of well-known plants used in traditional medicine a very high percentage of useful drugs have entered modern therapy The same is true of the recent Chinese experience[5]. However given the situation in developing countries, standardized plant extracts should be by virtue of simplicity and relative economy have priority over the long-term objective of discovering new pure compounds with biological activity more desired by the modern pharmaceutical industry. Indeed it has been argued[1/3] that a chemically standardized extract can be therapeutically at least as effective as the active principle, and being relatively inexpensive could be prepared in the pharmaceutical industry of a developing country. To quote from the WHO Publication[1]:

> "There is therefore much in favour of establishing programmes for producing standardized and safe galenical traditional preparations for potential use in primary health care, with the eventual aim of discovering their active principles. Even if the active principles have not yet been identified in some of the plants used in Traditional Medicine historical evidence of the value of such plants could result in useful preparations provided they are safe. Evaluation of safety therefore should be a prime consideration even at the expense of establishing efficacy of the preparation."

Research and Development objectives and goals must therefore be determined with this consideration in view. In all ongoing UNIDO programmes; the build-up of a national R & D capability in a variety of disciplines such as botany, agro-technology, chemistry, pharmacy, pharmacology and process technology has been an overriding consideration.

3. PROSPECTS FOR ENDOGENOUS PROCESS TECHNOLOGY DEVELOPMENT IN THE DEVELOPING COUNTRIES.

3.1 Needs and Strategies

The development of a programme for harnessing the benefits from traditionally used herbal remedies can best be carried out in a milieu that includes the following elements:

- The socially accepted usage of herbal remedies
- The presence of some agrotechnological and botanical expertise
- The availability of some expertise in phytochemistry, pharmacology and pharmaceutics.
- Ongoing facilities for commercial scale formulation and packaging of pharmaceuticals

In a large number of developing countries there is obviously a prevalent usage of, and faith in, traditional plant-based remedies. However, any expertise in botany or crop-technology is confined to the respective specialised institutions such as Botanical Gardens, University Departments of Botany, Departments or Institutes of Agriculture, Forestry and Crop Research. It is also a fact that in developing countries researchers for the most part have concentrated their efforts on broad spectrum phytochemical or pharmacological screening of medicinal plants, and these have resulted in the identification of the chemical constituents within them, or the responses of plant extracts to specific or general pharmacological tests. Therefore very often the real assessment of the clinical aspects of plant species used in traditional medicines have tended to remain undetermined.

At the other end of the line, many developing countries possess facilities for commercial scale formulation and packaging of ethical drugs starting from pharmaceutical chemicals that are almost invariably bulk-imported. It is often the case in these developing countries that such facilities as have been installed have considerable excess capacity. This excess capacity could with some simple adjustments - and of course appropriate policy changes - be employed in the formulation and packaging of herbal preparations. This approach, however, would only be possible if technologies were available for processing plant material into a form suitable for formulation. the need, therefore, is that the expertise available within a developing country, in all the relevant desciplines, be oriented towards forming a nucleus for research, development and quality control to serve a programme of drug development using indigenous plant materials. This introduces the prime necessary of initiating and managing a multi-disciplinary very often inter-institutional, goal-oriented research programme within a developing country - not by any means an easy exercise.

This has been the approach and strategy underlying UNIDO's ongoing programmes in this area of activity.

3.2 Pilot plant Scale Technology Development

One of the major features in the successful execution of the strategy just described has been the servicing of the obvious need in developing countries viz. the facility for process technology development. this has been accomplished by the acquisition and installation of a versatile poly-functional pilot plant withthe capability to carry out a number of unit operations such as the following:-

- Cominution of plant material (crushing, pulverizing to the appropriate dimension)
- Percolation with water or organic solvents at ambient as well as higher temperatures
- Batchwise aqueous/aqueous-alcoholic extraction
- Continuous extraction with organic solvents
- Removal of solvents and solvent recovery

- Drying of products
- Steam distillation of volatile constituents
- Separation of volatile, water-immiscible oils
- Filtration and purification by crystallization
- Fractional distillation.

No standard models of such pilot plants with the capability of carrying out a multiplicity of unit operations such as the above are readily and inexpensively available commercially. Several specialized manufacturers have offered acceptable designs which have been constructed when specially ordered based on UNIDO's specifications (Annex 1), and in UNIDO's experience only one such commercial design substantially meets the technological requirements.

Generally such pilot plants range in capacity from those able to deal with 80-100kg of plant material per charge to larger ones of over 3-4 times that capacity. the cost of procurement and installation ranges from 80,000 dollars to 150,000 dollars in today's terms, and this is quite prohibitive to developing countries when not assisted by international funding.

The acquisition of such a pilot scale processing facility in a developing country would be the king-pin in the mechanism of a drug development programme utilizing indigenously produced plant species. The pilot plant could be used to develop suitable technology and to produce sufficient processed material for chemical work, biological testing, standardization and formulation experiments and even for the conducting of preliminary clinical trials.

Accordingly it seems obvious that UNIDO should itself develop the design of such a pilot plant with suitable variants and options that should suit the developing country situation.

3.3 The proposed Versatile Polyfunctional Pilot-scale Processing Unit

The most satisfactory answer to the problem identified here is the design of a versatile polyfunctional pilot-scale processing plant by UNIDO taking into consideration the following factors:

- The Pilot-scale Processing Plant should have the facility to carry out the various processes previously outlined
- It should be characterized by simplicity of design construction, installation, operation, maintenance and repair.
- Modular construction should be preferred whenever feasible so as to enable increase of capacity as well as function, by merely duplicating modules. Such construction should enable a developing country to commence work using a module with a capability in only a selected range of the unit-operations and add on more sophisticated capabilities later.

- Standardized and optimized process control and measuring units, pumps and other ancillaries, should be employed for facile replacement.

- All plumbing and electrical wiring should be designed for simplicity, utility and facility in repair and maintenance.

- Instructions for installation and operation and maintenance should be clearly outlined in a detailed Working Manual included in this package.

Such a Versatile Polyfunctional Pilot-scale Processing Plant if developed by UNIDO as a detailed design will, besides serving the needs of a drug development programmes in developing countries, have the following additional advantages:-

- It will be ideal for developing country needs in the context described, as well as to serve in the production and processing of other economic plant-derived products.

- It will enable comparisons to be made between offers for construction and supply, made by various suppliers, when procuring the package.

- It will enable developing countries with adequate facilities to construct the equipment themselves, for their own needs or for export to other developing countries.

- It will minimize costs in installation, start-up and validation of equipment.

- Manpower training process technology and exchange of such expertise will be facilitated.

- It will stimulate developing country designers and technologists to embark on design improvement adaptation and innovation.

- The modular construction could enable two levels of capacity to be provided without too much design change.

In particular, such a package will be the centre-piece for a goal-oriented drug development programme.

4. PRODUCT STANDARDISATION, AND EXPORT POTENTIAL

4.1 Quality Control and Formulation

The Pilot Plant-Scale technology development must be supplemented and supported by modern analytical instrumentation for quality assessment, as well as laboratory scale formulation equipment, so as to serve the purpose of a drug development programme such as has been described. In the case of several developing countries, the facilities of already existing institutions can and should be suitably augmented and oriented to serve as R & D and quality control units, and to conduct biological as well as formulation studies.

Pilot-plant technology is needed for development of process technology and for determining a variety of techno-economic parameters needed for a relevant feasibility study, prior to commercial batch scale processing, followed by clinical assessment and marketing. This has remained to most developing countries the great impasse which UNIDO programmes have contrived to overcome. However, such programmes will remain with limited impact unless and until there can be developed standardized products which are suitable for indigenous health care programmes and products with a quality assurance acceptable in international trade which could generate foreign exchange.

The quality assessment of products is therefore a major concern as is the formulation of suitable drug delivery forms from plant extracts for indigenous use. The regulatory requirements for the admission of such products into local therapeutic usage is largely a matter for the national ministries of health, but analytical profiles, and toxicological parameters will have to be determined prior to acceptance, and these would help in establishing both creditibility and acceptability. Rigorous quality control requirements precede acceptance of plant extracts, isolates and pure phytochemicals in international trade.

4.2 Prospects for Export Products from Development Countries

One of the more interesting prospects for a nascent industry in developing country is to be in a position to generate products which are exportable in addition to products for local use. Finished formulated drug forms will find little prospect of being accepted in the industrialized countries as they would face formidable regulatory barriers with demanding requirements of clinical, preclinical and analytical data. The costs of acquiring such data on their products will be virtually beyond the reach of developing country resources. Oftimes, their validity particularly for plant-derived products with a long history of usage may not be as relevant as in the case of synthetic chemicals. However, it is a fact that such regulatory barriers do exist and hence for the production of such finished products a developing country will be obliged to go into a partnership with an industrial concern in the developed world, to secure both resources, know-how, and ready market acceptance.

Yet there is the possibility that developing countries would be in a position to export to the industrialized countries semi-processed products such as total extracts, partly purified extracts, essential oils or even pure natural products. For example a list of plant-derived drugs procurable from developing countries has been recently published by WHO[1]. A similar array is represented in the list compiled by UNIDO[4]. It would perhaps be UNIDO's role in encouraging industialized countries to seek to acquire such products from developing countries. In this the industrialized countries could clearly lay down their requirements, and make available to prospective developing country suppliers, specifications and standards for products in terms of modern analytical data. Such a course would be of doubtless benefit both economically and from the viewpoint of health-care programmes to both North and South.

There are many new areas of health-care that are yet in need of therapeutic agents, and such agents in the future may still be derived from plants. For instance, new natural products described as "Adaptogens" and

Immunostimulants" are expected to be increasingly employed as therapeutic agents[5/] in the future. It is therefore possible that supplies of both raw materials as well as partially processed medicinal plant-products would be needed by industrial concerns in the developed world. Where such are needed one can easily understand the supply problems of industry both in terms of adequacy of quantity and quality. Agreement as regards quality standards that are applicable and expected, will help considerably, both developing countries as suppliers and industrialized countries as consumers of such products. Accordingly, the development of internationally recognized standards based on modern analytical parameters, product by product must be a priority objective. It is clear that many developing countries would be in a position to supply quality assured standardized products in the future and this would be a cost effective exercise beneficial to all parties.

UNIDO could play a role in multi-lateral arrangements leading towards such a marketing pattern.

5. CONCLUSION

The following emerge as the issues from the considerations discussed in the foregoing sections, and are commended for the attention of the consultation.

Firstly, Industrialised countries should seek to import their requirements in raw materials and plant-derived products from developing countries. To facilitate this, industrialised countries could make available - through UNIDO - their requirements, as well as the standards and specifications applicable for plant raw materials, and partly or fully processed plant-derived products, imported by their industry.

Secondly, Developing countries should seek to produce not only raw materials but as far as possible partly processed plant-derived products to the specifications and standards demanded by the industrialised countries. In order to deliver to the international market products up to acceptable specifications and standards and so as to promote greater processing capability within developing countries, UNIDO proposes the design and development of a pilot plant with versatile capability particularly suited to the needs of developing countries for industrial utilisation of medicinal and aromatic plants as the basis of quality assessment of both raw materials and products.

Finally, UNIDO promote, in collaboration with organizations such as the International Standards Organization, the formulation of Internationally recognised quality standards for pharmaceuticals which are plant raw materials or plant-derived, that could form the basis for North-South trade (on a bilateral basis) in these materials.

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ANNEX 1

Specifications for a Versatile Poly-functional Pilot Plant Assembly for handling Medicinal and Aromatic Plants

PLANT CAPACITY
Model I - Capacity 80-100 Kg per charge, dry weight basis
Model II - Capacity 150-250 Kg per charge approx. on dry weight basis.

1. Characteristics of Raw Material to be processed

Plant material, (leaves, woody stems, barks, wood, roots rhizomes, fruits, nuts, whole shrubs - usually in dried condition).
Density of material between 0.2 - 0.3.

2. Products to be made

Aqueous extracts; Dried extracts.
Solvent extracts (polar and non polar solvents of a volatile and inflammable nature, as well as those which may be toxic e.g. benzene).
Alcoholic and aqueous alcoholic extracts steam distillates of essential oils.

3. Specific operations to be carried out

- Comminution of plant material (crushing, pulverizing to the appropriate dimension)
- Percolation with water or organic solvents at ambient as well as higher temperatures
- Batchwise aqueous/agareous alcoholic extraction
- Continuous extraction with organic solvents
- Removal of solvents and solvent recovery
- Drying of products
- Steam distillation of volatile constituents
- Separation of volatile, water-immiscible oils
- Filtration and purification by crystallization
- Fractional distillation.

4. **Major components of the pilot plant assembly**

		Minimum Quantity	
1.	Extractor vessel Fitted with heating device (steam jacketed) inside working pressure: atmospheric. Loading device including perforated grids or wise-mesh basket.	1	
2.	Heat-Exchanger (condenser) - (Tubular Type) suitable for solvent recovery and distillation of essential oils	1	
3.	Florentine vessel for separation of oil heavier than, and lighter than water	1	
4.	Reduced pressure solvent evaporation system: Reboiler with matched capacity (or design possibility to utilise extractor vessel itself) with steam heating device. (include one packed column with reflux exchanger, colling device, receiving vessel with matched capacity and a safety filter for miscella)		
5.	One compatible vacuum pump with explosion proof motor		
6.	Cussher - capacity approx.	30-50kg/h	Model I
		100kg/h	Model II

NOTES

Note 1:

All pipelines and valves and all parts of the pilot-plant assembly in contact with solvent or product to be of high grade stainless steel. Water and steam pipelines may be of galvanised steel or other suitable material.

Note 2:

All service requirements and other information to be clearly indicated as follows:-

(i) Steam consumption kg/hour
(ii) Water consumption m^3/hour
(iii) Scaffolding and foundation requirements
(iv) Dimensions of assembly and layout plans
(v) Line diagrams of all individual items and total assembly.