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ASSISTANCE FOR THE PRODUCTION OF PLANT DERIVED PHARMACEUTICALS

DP/URT/81/026

TANZANIA

Terminal report*

Prepared for the Government of Tanzania
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of Mohammed Alauddin, expert in medicinal/aromatic plants processing

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I EXPLANATORY NOTES AND ABBREVIATIONS

A. Explanatory notes

- The text of the report has been kept brief but has been adequately supported by self explanatory tables, and graphics.
- The observations and findings are based on limited statistical data and require further studies to arrive at more realistic figures.
- The activities of the previous experts mission have only been referred in the present write-up and relevent reports must be consulted for details.
- Metric weights and measures have been used throughout the report while United States Dollars have been employed as international currency.

B. Abbreviations

P.D.P. Unit	:	Plant Derived Pharmaceuticals Unit.
T.M.R.U.	:	Traditional Medicine Research Institute.
M.M.C.	:	Muhimbili Medical Centre.
K.P.I.	:	Keko Pharmaceuticals Industries.
C.M.S.	:	Central Medical Stores.
N.C.I.C.	:	National Chemical Industries Corporation.
U.N.D.P.	:	United Nations Development Programme.
U.N.I.D.O.	:	United Nations Industrial Development Organization.

II ABSTRACT

Project title

Assistance for the production of plant derived pharmaceuticals.

Project number and purpose

DP/URT/81/026.
Utilization of the indigenous natural resources of medicinal and aromatic plants for the production of pharmaceuticals.

Objective

Commissioning of the pilot production unit and extraction/steam distillation of selected medicinal and aromatic plants.

Duration of the mission

4.5 months. split into following two phases :

	1st split mission	2nd split mission
Starting date	17 September 1986	8 July 1987
Completion date.	30 November 1986	7 September 1987

A. Evaluations and shortcomings

1. Evaluations.

a. National staff: Staff of the P.D.P.unit is well qualified and has now been trained to operate all systems satisfactorily.
Similarly, various functions of T.M.R.U. are also adequately staffed with well qualified personnel, most of which are reasonably experienced in respective fields of research.

b. Equipment: The P.D.P. unit installation is composed of multi-purpose machinery which has been commissioned during first phase of the mission. All sections of the system are operational and performance is generally satisfactory. the technology of three basic processes alongwith the side line processes, for which this system has been designed, have been successfully achieved.
The T.M.R.U. laboratories, which are designed to cover research in all aspects of medicinal plants sciences are well equipped for this purpose with modern and sophisticated equipment. Most of these equipment, however, are as yet to be utilised to any reasonable extent.

2. Shortcomings :

a. National staff

. Only one pharmacist has been trained to operate the P.D.P. unit and the unit cannot be operated by the support staff in absence of the pharmacist.
. The T.M.R.U. personnel need leadership and coordinated monitoring of work to attain meaningful progress.

b. Equipment :

. The P.D.P. unit has been designed for production of tinctures, liquid extracts and essential oils. Additional machinery will be required to broaden the product range and to widen the processing techniques.
. T.M.R.U. is generally short of bench scale glass ware, accessories, laboratory supplies and chemicals/solvent normally required for phytochemistry and allied research work.
. Production of quinine sulphate from cinchona bark will need a new set of equipment housed in an altogether separate building adjacent to P.D.P. unit.

B. Recommendations

The recommendations included in the main body of the report are aimed towards the following objectives :

1. P.D.P. unit.

   . Improvement in performance efficiencies and operational capacities.

   . Enlargement of product range and diversification of technological capabilities.
   . Establishment of systems aimed at efficient and productive operation.
   . Institution of on-the-job and external training programmes.

2. T.M.R.U.

   . Improvement in the working facilities.
   . Development of effective leadership for coordinating various functions of the unit and achievement of the objectives.

3. OTHERS.

   . Creation of specialised cell at P.D.P.Unit to organise and establish systems for forecasting, procurement and sales.
   . Preparation of techno-economic study for indigenous production of quinine salts from cinchona bark

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IV INTRODUCTION

A. Project Background

Efforts towards utilization of natural flora for production of plant derived pharmaceuticals in Tanzania were initiated in 1977 when UNIDO organised an exploratory mission for collection of information and basic data on medicinal plants found in the natural habitat. This was followed by a visit of the mobile unit of UNIDO experts in 1980 to collect samples of medicinal and aromatic plants for quality evaluation and to demonstrate techniques for production of galenicals/plant derived pharmaceuticals from the plants available in commercial quantities.

Based on the encouraging findings during these missions, a UNDP/UNIDO assistance project was ultimately formalised in 1982 to establish a multipurpose pilot scale facility for production of plant derived pharmaceuticals with allocation of the following financial inputs :

1. Government input TAS 1,710,000 (Non-convertible)
2. UNDP input $ 223,000 (Convertible)

The government inputs covered the costs towards buildings, and experimental plantation of 38 exotic plants, seeds for which were provided by the UNIDO expert in agronomy during his visits in 1980 and 1983.

The UNDP input was comprised of pilot scale production machinery for galenicals and essential oils, laboratory equipment, international experts, national staff training and a field work vehicle.

Experimental plantations were undertaken at four different geographical locations totalling about 25 hectacres between December 1983 and March 1984. The results were generally promising except in few instances where damage was observed due to disease/heavy rains. Sizeable crops of seeds were also collected from several of the successful plantations. Upon accumulation of sufficient data on crop behaviour and optimum growth conditions by October 1984, plans were made to expand cultivation of the selected promising plants to ensure sufficient supply of material for processing at P.D.P. unit.

The multipurpose galenicals/essential oils production units was delivered and installed in 1984 but could not be commissioned due to non availability of electrical power supply at the site.

The technical assistance included expertise in agronomy, quality control and production technology. the agronomist was fielded for two months in 1983 to provide assistance in development of experimental farms while the expert in quality control was provided to T.M.R.U. for two months in 1984.

The fielding of the production technologist for the P.D.P. unit, to demonstrate the unit operations, to train the national staff and to carry out pilot scale production of galenicals and essential oil, was synchronised with the commissioning of the P.D.P. unit in presence of the manufacture's engineer in September 1986.

B. Official Arrangements.

(Present Mission)

. Duration of the mission 4.5 months

	1st split mission	2nd split mission
. Starting date	17 September 1986	8 July 1987
. Completion date	30 November 1986	7 September 1987

C. Contributions.

1. Government contribution		TAS 1,710,000
2. UNDP Contribution	(original : 1982)	$ 223,200
	(revised : 1986)	$ 296,939

(1 U.S.Dollar = approximately 50 T.Shillings :-January 1987)

D. Objectives

1. First split mission.

P.D.P. Unit.

- Commissioning of the unit.
- Demonstration of unit processes capabilities of the unit.
- Production of selected galenicals and essential oils.
- Training of the national staff.
- Identification of additional inputs in perspective of the objectives of the project.

2. Second split mission.

P.D.P. unit

- Performance review and trouble shooting.

T.M.R.U.

- Demonstration of techniques :-
  - Tablets dosage form developments from galenicals.
  - Methodology development for production of pure substances from crude drugs of botanical origin.
- Review of facilities and identification of areas of improvement.

V. RECOMMENDATIONS

A. Plant Derived Pharmaceuticals Unit.

1. National staff :-

   . Additional technically qualified pharmacist should be provided as assistant to unit incharge who should be fully trained to operate the unit independently.

2. Equipment.

   Following equipment should be added to the facility in order to provide capability in crushing wider Types of drugs into assorted physical states and to enable the unit to produce solid/powdered extracts :-

   . Crushing/grinding machine
   . Tray type vacuum dryer
   . Room dehumidifier.
   . Industrial vacuum cleaner.

   In addition, the ancillary items, utensils, manipolation and handling items and cleaning aids, identified during the present mission, should also be made available to the unit.

3. Utilities and Supplies

   . Steam supply of 20 kg per hour at a pressure of two bars should be ensured during steam distillation and vacuum distillation processes.
   . Water supply to the vacuum pump should be directly linked with the mains to ensure optimum efficiency.

4. Training

- The unit incharge should be given training in such aspects as work standardization, economics of production, personnel handling and materials management.
- The other staff should undergo inhouse training session covering operational procedures, good manufacturing practices and personal cleanliness and hygiene.

B. Traditional Medicine Research Unit.

1. National Staff

- No external training requirement could be identified at the present stage.

2. Equipment.

- Bench scale investigational and processing equipment, identified during the present mission (annex 1) which are essential for adequately equipped products development facility, should be immediately provided.

- Annual requirements of consumables like bench scale glassware, manipolation accessories, laboratory supplies and utensils and chemicals/solvents/reagents should be assessed and must be regularly provided through normal budgetary provisions.

3. Management.

- A systematic and coordinated programme, based on national priorities should be implemented for drug identification and evaluation on one hand and production process development on the other.

- Scaling up of processes methodology and economics of commercial production should be closely integrated with the process development objectives.

C. General.

- A centralised system should be evolved to coordinate the operation of the unit with those of K.P.I. and T.M.R.U. aiming towards national priorities.

- Sufficient administrative and financial authority should be vested with the incharge of the P.D.P. unit.

- The project vehicle should be alloted to the P.D.P. unit on full time basis.

- A separate cell, preferably in the premises of K.P.I. should be created to promote the produce of P.D.P., explore market, develop forecasts, and to organise procurements of raw materials and sales of the produce with particular emphasis on exports.

D. Production of Quinine Sulphate.

Based on the outcome of investigational work carried out at T.M.R.U. for development of a simplified process for production of quinine salts from cinchona bark a techno economic study should be prepared for establishment of a facility for production of pure therapeutic substances from medicinal plants.

In order to develop a meaningful techno economic study for indigenous production of quinine sulphate from cinchona bark, however, availability of reliable statistical data, based on the following quidelines is an essential pre-requisite in absence of which no proposal can be evaluated with respect to its economic feasibility

1. AVERAGE ANNUAL HARVESTING OF CINCHONA BARK.
   This should include quality specifications and total alkalaidal contents, current trading channels and means of ensuring procurement.

2. ANNUAL NATIONAL REQUIREMENT OF QUININE SALTS
   This should cover all pharmaceutical dosage forms and also consumption in foods and beverage industry.

3. CURRENT PRICES.
   This should include the export price range of cinchona bark and import price of respective pharmaceutical dosage forms as well as the bulk quinine salts including the import tariffs wherever applicable.

VI ACTIVITIES

In accordance with the schedule for fielding the expert in production technology in two split missions, allowing six months period for the national staff to operate the unit independently, the work plan was also split into two distinct phases (annex 2).

At certain occasions, however, the activities had to be altered in accordance with given circumstances and national priorities. these changes, however, did not result in deviation from the basic objective of the assistance.

A. First Split Mission

During the first three weeks work on certain activities, originally scheduled for the second split mission, was taken up at T.M.R.U. when the P.D.P. unit could not be commissioned due to delayed arrival of the engineer from machinery supplies and time consumed for construction of cubicle for main switch board in an isolated location. These activities, however, were resumed and completed during the second split.

The experience gained during the work at P.D.P. unit clearly points to the fact that mere material inputs in terms of building, machinery, and staff will not be adequate to deliver the projected achievement unless fully supported by inputs such as rationale planning , mobilization of necessary operating expenses and means of motivation of national staff. These considerations have been given due weightage in formulating the recommendations.

The P.D.P. unit was commissioned by 28 October 1986 having only about two weeks for trials and actual production,the vital activities of the mission, and in order to achieve satisfactory degree of operational achievement and training of national staff, the mission was extended for additional 13 days.

The protocol (annex 3) signed during the tripartite meeting, held on 28 October, includes the work carried out during precommissioning period as well as for the start up of various functions. In order to economise on time, the trial operations were by-passed and the unit was subjected to actual production runs right after commissioning.

The unit became fully operational on 27 October and actual production runs, to demonstrate the following technologies, were accomplished by 20 November.

- Production of essential oils through steam distillation.
- Extraction of crude drugs by Soxhelet method.
- Extraction of crude drugs by Percolator method.
- Solvent recovery methodologies.

The remaining period of the mission was mainly devoted to the training of the national staff in the following areas:

- Tail ending measures
- Final product handling
- Sideline processes
- Cleaning and maintenance.

Commissioning of the P.D.P. Unit

1. The Chopper : A high speed, heavy duty machine to chop fresh or dried leaves, whole herb and bark into 1 - 2 cm fragments.

   Material should be fed with moderate rate to avoid jamming of feeder roller and/or conveyor particularly in case of fresh drugs.

   Generates considerable air born particles of dried and lighter materials. Should be housed in more isolated position.

   Unsuitable for crushing small fruits, seeds and relatively harder materials and for finer mesh grinding.

2. The vacuum pump :Vacuum down to required level was attainable within few minutes with supply of water of 2 bars pressure and above but dropped quickly with decrease in water supply.

   Presently a common water line of one inch supplies both to condenser and the vacuum pump which is unadequate. An independent water supply for the pump is recommended to remove the present operational problem in distillation under vacuum when both condenser and vacuum pump have to be operated simultaneously.

3. The agitator (main still) Operater at about 50 revolution per minute and is satisfactory for the purpose.

4. Distillation (under normal pressure)

   Water: about 40 litres per hour. Further improvement possible by improving the steam supply.

Temperature of condensate about 50 deg (Cooling water temp: 31 deg C) Condensate temperature will drop when water at ambient temperature of 25 deg could be supplied.

5. Distillation (under reduced pressure)

Could not be realistically ascertained due to deficiency in supply of water.

6. Steam distillation

Chopped leaves of eucalyptus 15 kg.
Rate of distillation : 40 - 50 litres per hour with steam at 1.3 bars. Condensate temperature: about 50 deg C (cooling water temp: 31 deg C)

7. Over all evaluation of the system
The individual components of the unit are reasonably well functioning and the system as a whole is satisfactory for the operations it has been designed for. Preliminary assessments of plant capacities and production rates have been summarised separately.

From the engineering design and workmanship point of view, however, the unit is lacking in many ways which cause operational difficulties and inconveniences. Although these discrepancies are not of serious nature but all the same reflect adversely on the quality and finishing of the supply.

Most of the discrepancies/deficiencies were noticed only during actual production operations of the unit as prior to this the attention was entirely focussed upon expedient commissioning of the unit.

a. Deficiencies

i. Fabric sacks for Soxhélet (Reported in the protocol)
ii. Perforated bottom plate for percolator (Reported in the protocol)
iii. Valve control knobs for side glass tubes on soxhelet and sedimentation tank (four)
iv. Supply of Raschig rings for rectifying column.
v. Top vent in the Soxhelet.

b. Defective guages

i. Temperature guages both on the still and cool water supply (two)

c. Quality and standards

i. Side and bottom outlets of Florence flask and bottom outlets of percolator, Nutch filter, sedimentation tank and recovered soivent receiver are neither standardized according to usage nor machined to proper tapering and groved nozzles.

ii. Bolt and nuts used at certain positions are of variable sizes, where one standard size could have been maintained permitting standardised single set of tools for maintenance.

iii. Metal guard for the side glass tube of the sedimentation tank is grossly misalligned (caused breakage of two tube before it was detected)

iv. Stands for percolator and Nutch filter are too low causing inconvenience to operators.

v. Top cover, side and bottom joints of Florence flask are not properly alligned with the parent system.

Pilot Scale Production

1. Steam Distillation

In addition to trial steam distillation of 15 kg. of fresh eucalyptus leaves, three pilot scale steam distillations were carried out with gradual scaling up:

i.	Cardamom fruits (dry)	20 kg
ii.	Cardamom fruits (dry)	46 kg
iii.	Dracocephalum moldarica (fresh herb)	101 kg

With a steam supply ranging between 1.0 - 1.3 bars, the distillation was effectively complete between 75 and 60 minutes respectively with collection of about 40 - 50 litres of distillate (45 deg - 50 deg C).

The oil of Cardamom obtained in a yield of about 3.25 per cent was pale clear liquid. The sample is currently under quality evaluation at TMRU.

2. Soxhelet Extraction.

One tincture was produced.

Tincture Cynara scolymus 10% W/V (Solvent of extraction 95% ethanol)	100 litres

Being flufy and light in nature only 10 kg. of the dried chopped herb, (packed in a sack) could be loaded in the Soxhelet chamber which then required over 60 litres of solvent to effect one syphon cycle.

With a steam supply of one bar and above as distillation source one cycle was completed in about 90 minutes permitting five fold extraction in eight hours.

3. Percolation Process

One tincture was produced.

Tincture cardamom simple 13° W/V (Solvent of percolation 60% ethanol).	100 litres

After soaking the moderately fine grounded fruits in a covered container overnight in 60% ethanol (20 litres), it was packed in the percolator.

Rate of percolation was maintained at about 4 litres per hour and percolation completed in about 20 hours. A syphon installed on the percolator can permit uninterrupted percolation overnight.

Maintaining a flow rate of 3 - 5 ml/minute/kg of drug, the rate of production will depend upon the quantity of drug packed in the pecolator. With a load of 20 kg. of drug for instance, a rate between 100 - 150 litre per 24 hours can be achieved.

4. Solvent Recovery

About 200 litres of poorly stored stocks of 35 - 40% and 60% ethanol were reclaimed into 60% and 90% ethanols respectively in yields of about 90%.In absence of rectifying medium the results of recovery are fairly satisfactory.

Evaluation

1. Plant Capacities and Production Rates

a. Plant Capacities

The rated capacities and outputs of Individual components of the unit and service equipment are tabulated in annex 4. The annex also illustrates the variety of processes which can be carried out and identifies the equipment required for each process.

The percolation process can be simultaneously carried out along with any other single processing on the main assembly offering the possibility of production of two products at one time especially the steam distillation, which does not need feed from percolator.

The vacuum dryer,the last item on the list, which has not been provided, is essential for production of solid/powdered extracts.

b. Production Rates

In view of rather scanty data on the actual production runs collected so far, it is premature to ascertain the outputs of various processes realistically and the production rates computed at this stage, therefore, should be considered merely as fair approximations:

PROCESSING OPERATION	LOAD RANGE	RATE
1.Materials Crushing	Continuous	200-300 kg per hour
2.Steam Distillation	100-200kg	60 litres per hour
3.Percolation	10-20kg	3.5-5.0 litres per hour
4.Soxhelet Extraction	10-20kg	60 litres per hour
5.Filtration	Continuous	Fast(Not monitored)
6.Solvent Recovery	100-300 litres	70-80 litres per hour

2. Operational limitations

a. Crusher : Not suitable for small size seeds, fruits, hard bark and for powders (smallest particle size possible is about 10 mm).

b. Percolator : Light weight and flufy drug cannot be processed in more than 15 kg. quantity.

c. Soxhelet : Light weight and flufy drug cannot be processed in more than 10 kg. quantity. Production of tincture of Cynara Scolymus 10% W/V, requiring 100 litre final volume adjustment demanded constant vigil to maintain adequate volume of solvent in the still because the extractor required over 60 litres of solvent to effect the syphoning. (Soxhelet process is suitable only for extraction with undiluted solvent because the strength of required alcohol dilution cannot be maintained during extraction.)

d. Nutch Filter: Receiving chamber has capacity of only 30 litres which is sufficient for fluid extracts but filtration of tinctures can be carried out only in lots of about 30 litres requiring periodic interruptions.

e. Florence Flask : Cleaning of the flask requires total dismantling of top cover which is cumbersome and time consuming.

B. Second Split Mission

During the second split mission (8 July - 7 September 1987) the work was almost entirely centred at T.M.R.U. in accordance with the activities covered under section D and E of the work plan.

In view of the observation that neither any work was undertaken at the P.D.P. unit during the proceeding six months nor any supplies of crude drug was available for fluid extract production, no meaningful work was possible under A and B sections of the work plan. On the other hand the activities under section C were considered premature particularly in view of the keenness on the part of the government for development of a process for indigenous production of quinine salts from cinchona bark at P.D.P. unit.

T.M.R.U. is pursuing a multipronged master plan for exploitation of medicinal and aromatic plants with particular emphasis on the herbs used in traditional medicines in Tanzania and other countries.

The activities of T.M.R.U. are channelled in the following directions :

a: Experimental plantation of selected exotic medicinal/aromatic plants (annex 5)

b: Promotion of large scale cultivation of promising exotic and naturally occurring herbs of commercial value.

c: Chemical studies and pharmacological screening.

d: Development of standards of quality.

e: Clinical evaluation of new products from traditional and exotic herbs.

f: Process technology development.

The approach, combining fundamental investigations and research with applied work towards development of economically viable commercial products of established demand, offers a sound foundation to T.M.R.U.

Annex 5 also illustrates the schedule of work which is currently being followed for development of processes for production of plant derived pharmaceuticals and essential oils from a variety of locally available as well as recently cultivated exotic herbs.

In order to ascertain the quality of incoming supplies, to monitor the process efficiencies and yields and to guarantee the standards of outgoing finished products, however, a well organised and highly disciplined operation is mandatory. Similarly the work towards development of process technologies for new products require dedication and perseverance more than the facilities.

The current mission has allowed to make the following observations :

- The experimental plantation work has progressed well and has cleared the way for expanding the selected plantations on commercial scale.

- The operational facilities and working climate at T.M.R.U. require considerable improvement and managerial attention in order to draw optimum benefits from this modern and well equipped establishment.

  The short comings include absence of effective leadership and scarcity of personnel motivation and sense of direction.

In the limited time available the efforts were exclusively directed to reach at some meaningful guidlines for development of methodologies which could be used as basis for perfecting processes for large scale production of pharmaceutical dosage forms and pure therapentic substances from herbs. The approach was also beneficially employed as a tool for training of the national staff in bench scales skills towards products development technolgies:

- Production of galenicals from new herbs.
- Convertion of galenicals into pharmaceutical dosage forms.
- Production of pure substances from crude herbs.

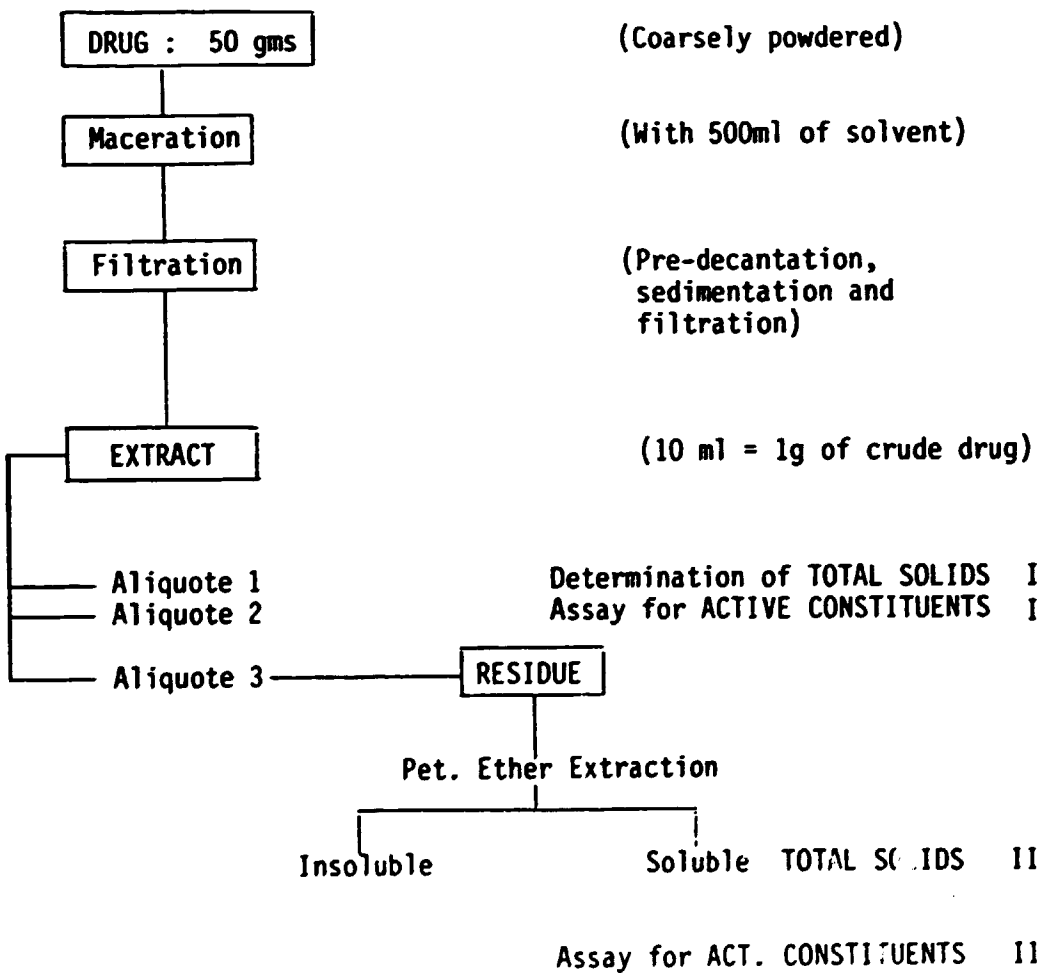
For the purposes of actual work the following products were selected :

- Extract of Cynara scolymus
- Tablets of Cynara scolymus
- Quinine sulphate from cinchona bark.

Production of galenicals from new herbs

The investigational work, briefly described hereunder, was partly carried out during early stage of the first split mission but has been included here for the sake of relevancy and corelation with the work carried out at T.M.R.U. during the second split mission.

Initially an exercise was worked out for screening various solvent systems in order to identify most efficient system to extract the drug with minimum cost. the scheme of work is outlined as follows :-



The exercise was designed to provide the following information:

- Comparative extraction efficiency of various solvent systems.
- Comparative active constituents extraction capabilities.
- Lipoid soluble components of the active constituents.
- Total fatty matter in the extractive.

Production of galenicals is, almost exclusively, carried out through extraction with alcohol, varrying in strength depending upon the nature of the active constituents extracted. The literature review lead to the following observations :-

Alcoholic strength with aqueous dilution.

Drug constituents	Mostly	Occasionally	Rarely
1.Alkaloidal	60-70%	40-45%	25% and 90%
2.Glycosidal	60-70%	-	45%
3.Essential oils	85-90%	60%	-
4.Oleoresinous	90%	70%	-
5.Saponaceous mucillagenous etc	45%	-	60%

The following exotic herbs now growing well at the experimental plantation, were investigated under the scheme of work illustrated earlier.

1. Cynara scolymus : Rutin
2. Calandula officinalis : Carotenoids
3. Glaucium flavum : Alkaloids

For demonstration purpose, three experiments were carried out for each herb employing 45 per cent, 60 per cent and 90 per cent alcohol as solvent of extraction.

The exercise was proved useful in so far as training of the national staff and development of a final procedure for production of tincture and fluid extract of Cynara scolymus was concerned but could not be carried out fully in case of Calendula officinalis and Glaucium flavum because of non availability of facilities for accurate gravimetric determinations and assays, which were vital for such work.

Production of pharmaceutical dosage form from galenicals

To demonstrate a technique for convertion of a crude drug extract into tablets dosage form, the tincture of Cynara scolymus, produced at P.D.P. on large scale, was converted into a fluid extract by vacuum distillation. At this stage an aliquote of the extract was triturated with a variety of "carriers" followed by vacuum drying to obtain a material capable of conversion into granular powder, which could be processed further for production of compressed tablets employing classical methods for production of tablets.

In case of the above experiment, calcium carbonate was finally selected as carrier/diluent based on the preferance shown by the medical profession. Pulverised talk offered better results but was considered pharmacologically unacceptable.

Based on the recommended dose of 2 gm of dried crude drug, which yields 6.0 per cent extractive on dry basis the following qualitative/quantitative formula was evolved for Cynara scolymus tablets :

Each tablets contains :

1.	Extract Cynara scolymus		120 mg (on dry wt basis)
2.	Calcium Carbonate	(B.P.)	438 mg (fine powder)
3.	Talcum	(B.P.)	71 mg (Lubricant)
4.	Starch	(B.P.)	71 mg (disintegrating agent)
5.	Alcohol	(B.P.)	QS
6.	Water		QS

Tablets were compressed using round biconcave punches of about 10.0 mm diameter on a laboratory scale press at an average weight of 700 mg and with hardness ranging between 8-10 kg.

The tablet, well shaped, smooth and light brown in colour and each representing 2.0 gm of dried leaves of cynara scolmymus, passed the physical tests for weight, hardness and friability and had a disintegration time between 10-12 minutes.

Production of quinine sulphate from Cinchona bark

The manufacture of quinine from cinchona bark is carried out employing numerous classical routes (Annex 6) for extraction of cinchona bark. The work at T.M.R.U., however, was taken up for the following reasons :-

- Use of kerosene as solvent for extraction as it was considered economical and more easily accessessible in the country.
- Modification of the classical method so that the P.D.P. unit machinery could be employed for the manufacture of quinine sulphate as well.

Kerosene as solvent of extraction

T.M.R.U. furnished outline of a method for manufacture of quinine sulphate through extraction of chichona bark with hot kerosene in a yield of 4.0 per cent with information that the procedure is successfully used by a company in India.

Cinchona alkaloids being practically insoluble in alphatic hydrocarbon solvents in general, it was considered desirable at first to conduct an extraction capability study with kerosene as compared to benzene and toluene, the classical solvents for extraction.

In absence of adequate analytical facilities, the determination of exact alkaloidal contents of the bark employed for these studies was not possible and as such the optimum extraction efficiency of kerosene could not be ascertained. It was, however, confirmed that the extratability of the alkaloids by kerosene was considerably lower than benzene or toluene under parallel extraction conditions while the cost of recovery of the kerosene, having a boiling range of 150 deg - 325 deg C, would be much higher than benzene and may requrie an altogether separate distillation unit designed for distillation of high boiling solvents.

During the course of this study, the following observations were made :-

- Extraction with kerosene at 100 deg C yielded about 3.5 per cent alkaloids from the bark.
- More than 85 per cent of the alkaloids rapidly percipitated out of kerosene extract upon cooling in the form of buff coloured semi crystalline solid.
- The precipitated alkaloidal crude was practically insoluble in kerosene and only partially in benzene
- The alkaloidal crude could be converted into pure crystalline quinine base, after charcoaling a hot solution, from benzene in almost 90 per cent yield.
- Treatment of the alkaloidal crude with equivalent quantity of dilute sulphuric acid resulted in conversion to almost pure crystalline quinine sulphate in a yield of about 100 per cent.
- Thin layer chromatography on alumina, employing several recorded solvent systems, showed single bright violet spot (under U.V.light) of quinine using pure quinine base as standard reference.

Benefitting from these observations a simple procedure for production of quinine sulphate was evolved and was repeatedly experimented upon at T.M.R.U. (Annex 7). The procedure is merely a modification of the classical method. After liberation of the bases by treating the bark with dilute sodium hydroxide in presence of slaked lime, the differential solubility of alkaloidal mixture in kerosene at 100 deg C and at room temperature was successfully exploited to obtain a crude by cooling the hot extract followed by one step conversion to pure quinine sulphate.

Advantages

- Apart from the extractor, the subsequent steps require very simple equipment.
- Simplicity of the process allows possibility of production at scaled down levels economically.
- Offers an opportunity of commencing production through a battery of laboratory scale extractors, without sustaining the time lag for establishment of commercial facility.

Disadvantage.

* The product yield is expected to be considerably lower than the classical methods.
* The cost of the product may not remain favourable. This aspect, however, require detailed studies to reach a definite conclusion.

P.D.P unit and production of cinchona alkaloids

The P.D.P. unit has been designed specifically for production of galenicals and essential oils from medicinal and aromatic plants respectively. Certain quarters, however, were of the view that production of cinchona alkaloids was most probably possible in this installation.Accordingly a careful evaluation of the machinery vis-a-vis the steps involved for processing cinchona bark and its subsequent alkaloidal extract confirmed that none of the following stages of processing can be performed on the existing units.

- Digestive extraction under reflux followed by efficient separation of the extract from the "mark"
- Liquid/liquid extraction using dilute sulphuric acid.
- Crystallization and recovery of the finished product.

There is no alternate to hot extraction of the bark which is a key step in production of quinine salts as it guides the product yield and determines the ultimate economic of the process. In case of the suggested new method employing kerosene, maintenance of conditions are more critical because if alkaloids crystallise out of the extract either before or during removal from the mark their reclamation will be practically impossible.

In its present configuration and design,the P.D.P. unit at best can be employed for only solvent recovery. It is, however, possible to modify the main still so as to use it as extractor but the work will require major engineering involvements and as such it would be preferable to built a separate facility for this purpose. In the meantime laboratory scale production of quinine sulphate, following the suggested method, can be planned to process 5 - 10 kg of the bark on daily basis offering annual supply of 60 - 120 kg of quinine sulphate. Such a set-up would be equipped with the following :-

- Ten open mouth cylindrical stainless steel container of 5 litre each.
- A battery of ten laboratory scale hot extractors, suitably designed and with capacity of extraction one kg of the bark in one charge.
- Twenty containers of 6 litre capacity each for receiving and cooling the extract
- Glass flasks for dilute sulphuric acid treatment
- Two Buckner filter system with funnels of 25-30 cm dia and flasks of 10 litres..
- Four crystallization flasks of 1 litre capacity each.

After collection of sufficient quantity,the spent solvent could be recovered at P.D.P. unit under vacuum distillation in presence of water to salvage the small quantity of alkaloids remained in the spent solvent.

Time limitation did not permit experimentation of the suggested method using high boiling (100 deg - 120 deg C) petroleum fraction as an alternate of kerosene. If proved successful, this solvent is expected to be far more convenient to recover and at the sametime conveniently and economically available through contractual arrangement for supply from the state owned petroleum refinery in Dar-es-Salaam.

C. Additional Inputs

In order to strengthen the national capabilities towards indigenization of production of plant derived pharmaceuticals and pure substances and to overcome the current operational difficulties

and the short comings enumerated in Chapter II, following additional inputs are recommended :-

1. Expert assistance

Traditional Medicine Research Unit

. Expert in pharmacological research and screening	6 m/m
. Expert in plant derived pharmaceuticals studies	6 m/m

Plant Derived Pharmaceuticals Unit

. Expert in pharmaceutical industry for designing a facility for production of quinine sulphate with complete terms of reference.	6 m/m
TOTAL	18 m/m

2. Training

Plant Derived Pharmaceuticals Unit

. Plant derived pharmaceuticals and galenicals production technology 3+3	6 m/m
. Orientation and study tour for the national project coordinator	1 m/m
TOTAL	7 m/m

3. Equipment

Traditional Medicine Research Unit

. Laboratory instruments etc (annex 1)	$ 10,000

Plant Derived Pharmaceuticals Unit

. Additional machinery (Page 9)	$ 25,000
. Machinery for production of quinine sulphate.	$ 35,000
TOTAL	$ 70,000

DP/URT/81/026 Annex 1

Assistance for the Production of Plant Derived Pharmaceuticals
PROCESS DEVELOPMENT LABORATORY EQUIPMENT (T.M.R.U.)

a. Equipment

1. Grinder, kitchen type heavy duty, for variety of dried herbs	One
2. Laboratory steam generator, high capacity	One
3. Steam distillation unit 1-2 kg capacity	Two
4. Vacuum pump - dry centrifugal type	One
5. Dessicator vacuum	Four
6. Weighing balance, 1 kg capacity	One
7. Analytical balance - 0.001 gm accuracy	One
8. Refrigerator - 300 litre capacity	One
9. Spreading template for TLC and PLC	One
10. U.V. Spectrophotometer	One
11. Heating mantle - 3 litre R.B. flask	

APPROX. COST U.S.$ 6,000

b. Glassware

A. Flask, conical with stopper	1000 ml	12
Flask, conical with stopper	250 ml	12
Flask, conical with stopper	100 ml	12
B. Pipette Volumetric	100 ml	1
Pipette Volumetric	50 ml	3
Pipette Volumetric	25 ml	3
C. Cylinders graduated	500 ml	2
Cylinders graduated	250 ml	3
Cylinders graduated	25 ml	6

D. Funnel, separating, conical	1000 ml	3
Funnel, separating, conical	500 ml	3
Funnel, separating, conical	250 ml	6
Funnel, separating, conical	100 ml	6
E. Filtration assembly, Buckner	1000 ml	1
Filtration assembly, Buckner	500 ml	2
F. Dish evaporating, with cover, glass	100 ml	3
Dish evaporating, with cover, glass	50 ml	6
Dish evaporating, with cover, glass	25 ml	6
G. Pipette filler, standard peleus		2

APPROXIMATE COST U.S.$ 3,000

C. Reference standards of alkaloids, glycosides, steroids, polyphenols, sugars,--(to be identified at the time of indenting.)

APPROXIMATE COST U.S.$ 1,000

TOTAL COST U.S.$ 10,000

DP/URT/81/026 Annex 2

Assistance for the Production of Plant Derived Pharmaceuticals
OUTLINE OF WORK PLAN (First split mission)

Commissioning and Production

A. Commissioning of the Unit - P.D.P.

1. Performance of the chopper
2. Performance of the vacuum pump
3. Performance of the agitator
4. Distillation under atmospheric pressure (AP)
5. Distillation under reduced pressure (RP)
6. Distillation with steam
7. Over all evaluation of the system.

B. Pilot Scale Production - P.D.P.

1. Oil of Cardamom	Steam distillation
2. Tincture Cynara Scolymus	Soxhelet extraction
3. Tincture of Cardamom	Percolation.
4. Recovery of ethanol	Distillation at AP.

C. Evaluations - P.D.P.

1. Plant Capacities and Production Rates.
2. Operational Limitations

D. Preparation of interim report.

Annex 2 (Contd)

OUTLINE OF THE WORK PLAN. (Second split mission)

A. Review of the performance of the pilot plant P.D.P.

With particular reference to the following.

- Operation of the plant or any of its component.
- Production efficiencies and yields.
- Quality of the products manufactured.
- Adaptation of the technologies for new products.
- Scaling up of the processes developed at TMRU.

B. Commercial Production - P.D.P.

Production of fluid extract Percolation/Distillation (R.P)

C. Planning - P.D.P.

1. Sales/consumption assessments and production forecast
2. Raw materials management
3. Production planning and follow up
4. Work scheduling

D. Process Technology Development - TMRU

1. Economics of scale of production
2. Product costing
3. Demand level assessment and materials availability forecasting
4. Scaling up of process technologies.

E. Future Expansion

1. Priorities setting in conformity with national policies
2. Identification of additional inputs towards technical assistance, machinery and equipment and training.
3. Detailed proposals for production of pure substances from medicinal plants with priority for production of quinine salts from cinchona bark.

F. Preparation of final report.

DP/URT/81/026 Annex 3.

Assistance for the Production of Plant Derived Pharmaceuticals.

PROTOCOL

OBJECT. Project DP/URT/81/026 Purchase Order No. 15-3-12-053
Extraction Unit for Active Principles for Herbs
(Plant Derived Pharmaceuticals)
COMMISSIONING AND START UP TRIALS

Concluded this day of 28 October 1986 between :

Industrial Export import Romania	Represented by: Dipl.Ing.Vasilescu Jean
AND	
. Keko Pharmaceutical Industries	Represented by: R. Rwiza, Pharmacist Incharge.
. Traditional Medicine Research Unit (Muhimbili Medical Centre)	Represented by: M. Mshiu, National Coordinator.
. United Nations Industrial Development Organization that :	Represented by: M. Alauddin

(a) The components of the unit perform the assigned functions satisfactorily.
Optimum performance of certain functions, however, would be ascertained when the deficiencies in the supply of steam and water are rectified.

(b) In connection with the commissioning and start up of the unit, the following jobs have been accomplished between 28.9.86 -28.10.86.

1. PRE-COMMISSIONING STAGE : Annex 3 (contd)

(a) 1. Construction of a cabin for the main electrical switchboard, fifteen meter away from the processing unit, with reinforced concrete foundation.

2. Mounting of the switchboard in the isolated cabin.

3. Dislodging and withdrawal of the cable from the main unit.

4. Extension of some unit cable up to the main pannel.

5. Checking of individual cables with megameter and rectification of the faults.

6. Encasement of the cables in PVC pipe before earthing.

7. Grounding installation of the main electrical switch board.

8. Connection of the electrical board to the electrical network of the unit.

9. Step-by step checking of all electrical circuits.

10. Release of a starter switch, found rusty due to water seepage.

(b) 11. Reconditioning of the vacuum pump.

12. Adjustment and release of the chopper gear system.

II. START-UP AND TRIALS

1. (a) Unit-to unit blank checks for performance, vacuum/pressure maintainance, connections, seals, valves and leakages.

(b) Performance of vacuum pump, chopper and agitator

Annex 3(Contd)

2. TRIAL RUNS	REMARKS
a. Grinding of cynara scolymus (Not suitable for seeds & small fruits)	Satisfactory
b. Distillation of water/solvent at atmospheric pressure	Satisfactory
c. Distillation of water/solvent under vacuum	Satisfactory
d. Percolation of cardamom seeds	Material awaited
e. Steam distillation of cardamom seeds.	Material awaited
f. Soxhelet extraction of Cynara scolymus	Not carried out

III. MISCELLANEOUS

1. One of the explosion proof illumination tubes, installed under the platform, with a non-functioning transformer, has been removed.

2. The general switch of the Board TFL-i and the contactor A3 being out of order, have been replaced with the pieces loaned by Keko stores and will be replaced by the Industrial export import, Romania.

   The replacements was necessary because of following reasons :

a. Plastic lever of one of the three activators of the contactors in the general switch of the board TFL-i was found broken and the tension could be supplied only through two phase.

b. Upon activation of the push button on the door of the board TFL-i for tension of the 24v and lamps, the transformer was burnt out although the circuits were controlled with the megameter.

(C) IMPORTANT NOTES

The supply pressure of steam and ambient temperature and pressure of water at Keko do not meet the requirements, particularly the water supply for vacuum pump. In order to attain efficient functioning of the installation, for processes to be carried out under vacuum, it is essential that the supplies of steam and water be improved in accordance with the recommendations in the manual.

Proper and trouble free functioning of the unit also requires that the plant personnel must gain complete conversancy with the operating instructions, precautions an safety measures.

Sieve plate for the percolator and herb loading sack for the soxhlet have not been supplied by the Industrial Export Import.

Approved and signed on behalf of :-

1. Industrial export import :	(Dipl.Ing Vasilescu Jean)
2. Keko Pharmaceutical Industries Ltd.	(R.Rwiza, B.Pharm.MPST)
3. M.M.C.Traditional Medicine Research Unit.	(E. Mshiu, National Coordinator)
4. United Nations Industrial Development Organization.	(M. Alauddin)

DP/URT/81/026

Annex 4

Assistance for Production of Plant Derived Pharmaceuticals.

RATED CAPACITIES AND PROCESSWISE UTILISATION GUIDE.

PROCESS	RAW MATERIAL PREPARATION	EXTRACTION	CONCENTRATION	COLLECTION	TEMP. CONTROL	CLARIFICATION	DESSIC

PRODUCT \ CAPACITY	250kg/h	-	150L.	150 L.	400 L.	3 m^2	40 L.	100 L.	50 m^3/h	140 L.	200 L.	40 L.	20 Kg
GALENICALS													
TINCTURES	✓	✓	✓	-	-	-	-	✓	-	-	✓	✓	-
FL. EXTRACTS I	✓	✓	✓	-	✓	✓	-	✓	✓	✓	✓	✓	-
EXTRACTS I	✓	✓	✓	-	✓	✓	-	✓	✓	✓	-	-	✓
FL. EXTRACTS II	✓	✓	-	✓	✓	✓	-	✓	✓	✓	✓	✓	-
EXTRACTS II	✓	✓	-	✓	✓	✓	-	✓	✓	✓	-	-	✓
ESS. OILS	✓	✓	-	-	✓	✓	✓	-	-	-	-	-	-
RECOVERIES													
ATM. PRESSURE	-	-	-	-	✓	✓	-	✓	-	-	-	-	-
RED. PRESSURE	-	-	-	-	✓	✓	-	✓	✓	✓	-	-	-

Assistance for the Production of Plant Derived Pharmaceutical.

PRODUCTION PROGRAMME.

NO	PLANT.	FAMILY.	PL.PART	STATE	CONSTITUENTS.	STOCK (Kg)	DESIRED PHARMACEUTICALS.		
	I PHARMACOPEAL								
	Cinchona	Rubiaceae	Bark	Dry	Alkaloids	106.9	Qunine	Sulphate	-
	Cardamom	Zingiberiaceae	Seeds	Dry	Ess. oils	100.5	Tincture	-	Ess. oil
	Digitalis	Scrophulariaceae	W. H.	Dry	Glycosides	NIL.	Tincture	Extract	-
	Datura annoxia	Solanaceae	W. H.	Dry	Alkaloids	13 .0	Tincture	Extract	-
	II TRADITIONAL AND EXOTIC								
	Calandula officinalis	Compositae	Flowers	Dry	Carotenoids, phenols, saponins.	17.8	-	Extract	(for top.cream
	Cynara scolymus	Compositae	W.H.	Dry	Rutin	236.8	Tincture	-	-
	Glaucium flavum	Papaveraceae	W.H.	Dry	Alkaloids	-	-	Extract	-
	Saponaria officinals	Caryophyllaceae	W.H.	Dry	Saponins	-	Tincture	-	-
	Tagetes petula	Asteraceae	W.H.	Dry		32.0			

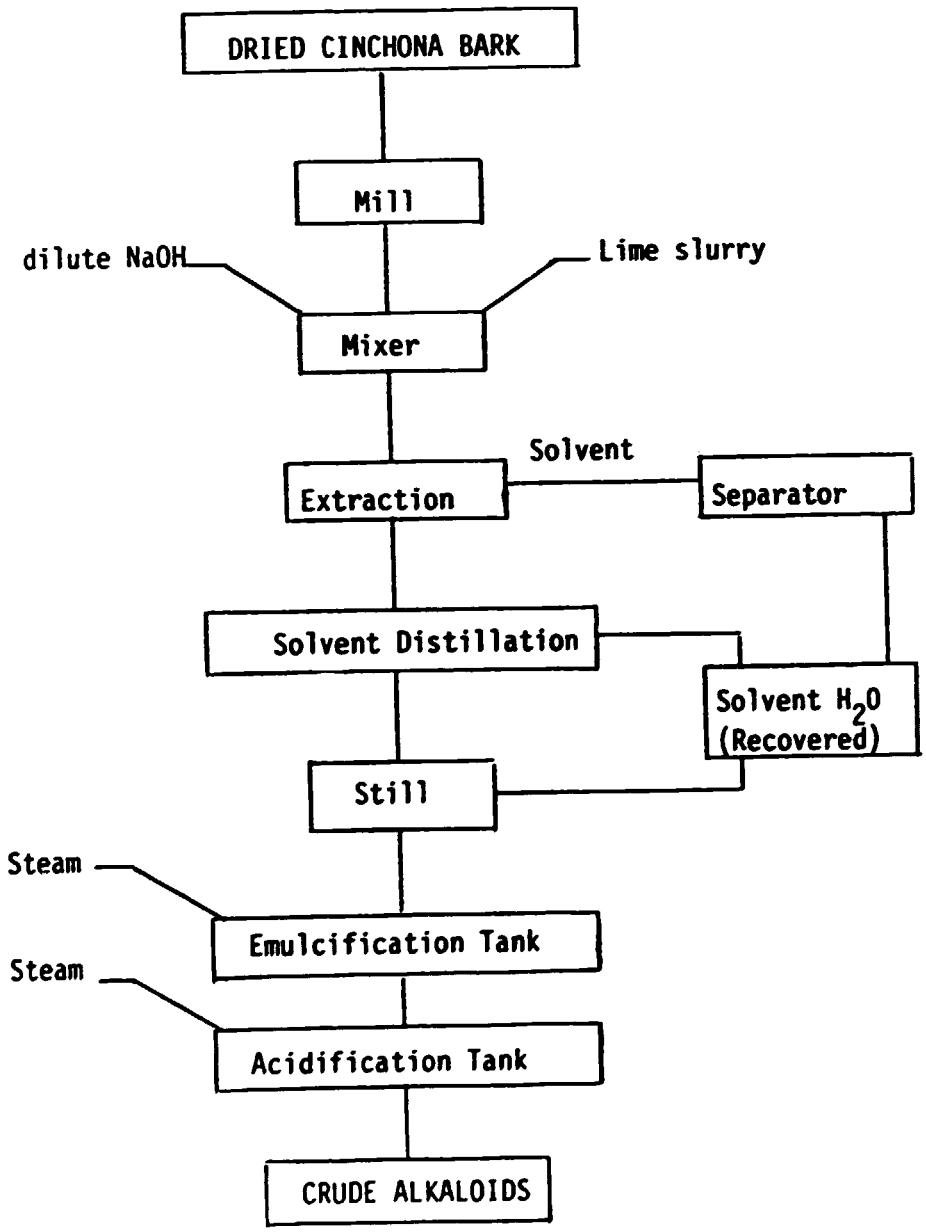
W. H = Whole herb; Ess. oil = Essential oil; top. cream = topical cream

DR/URT/81/026

Annedx 6

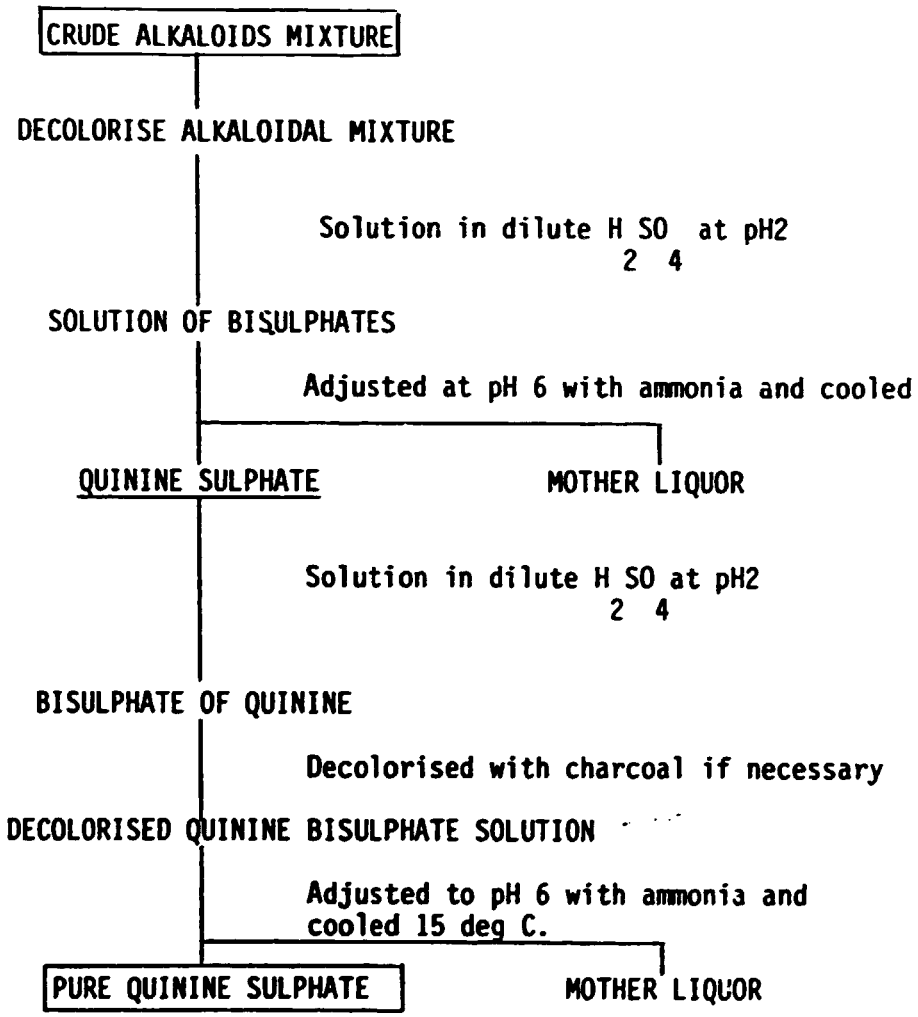
Assistance for the Production of Plant Derived Pharmaceuticals,
CLASSICAL METHOD FOR PRODUCTION OF QUININE SULPHATE FROM
CINCHONA BARK.

A. Extraction of crude alkaloids :-



Annex 6(Contd)

B: Production of pure quinine sulphate

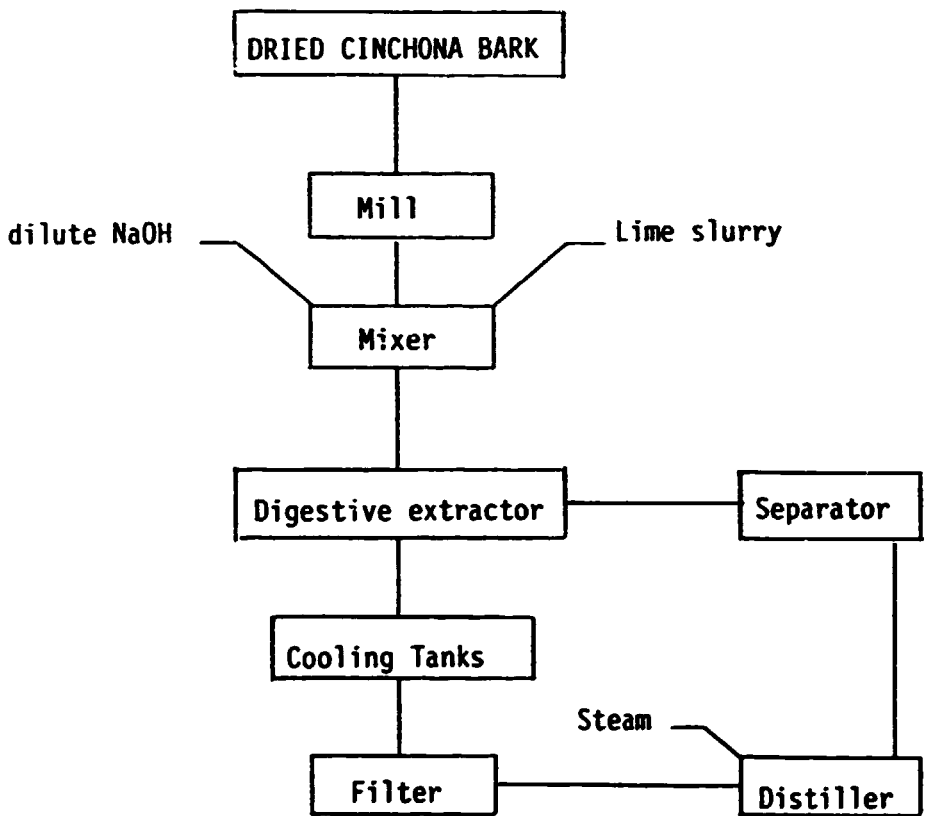


Alkaloidal materials recovered by alkaline treatment of the mother liquors to be processed separately for production of quinidine and other cinchona alkaloids.

DP/URT/81/026 Annex 7

Assistance for the Production of Plant Derived Pharmaceutials
A NEW METHOD FOR PRODUCTION OF QUININE SULPHATE FROM CINCHONA BARK USING KEROSENE AS SOLVENT

A. Extraction of curde alkaloids.



B. Production of pure Quinine sulphate :