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INDUSTRIAL UTILIZATION OF MEDICINAL AND AROMATIC PLANT RESOURCES FOR THE PRODUCTION OF PHARMACEUTICALS

US/GUA/84/282/11-01

THE REPUBLIC OF GUATEMALA

Technical report: Assessment of the laboratory results and develop schemes for pilot-scale processing*

Prepared for the Government of the Republic of Guatemala
by the United Nations Industrial Development Organization

Based on the work of E. Lörincz, chief technical adviser

Backstopping Officer: T. De Silva, Chemical Industries Branch

* This document has not been edited.

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I. INTRODUCTION

The report was written by Csaba Lőrincz (Hungary)

Duration : 10. February 1992 - 24. March 1992
Duty station : Universidad de San Carlos, Guatemala City

Purpose of project : Industrial Utilization of Medicinal and Aromatic Plant Resources for the Production of Pharmaceuticals

Job description (Annex I.)

A. ABSTRACT

Activities

1. Based on preliminary laboratory experiments we have prepared from four medicinal plants concentrated extracts by different solid-liquid extraction technologies.
   Production amount : 5 kg ground, dry medicinal plant.
   Extracting agent : 100% ethylalcohol.

2. From two medicinal plants essential oils have been produced for the purpose of gaining aromatherapeutic preparation.

3. Ten type of water-soluble (instant) solid, stable, medicinal product granulates having diverse compositions have been prepared.

4. Once a week I gave a lecture about industrial processing of medicinal plants. Material of the lecture had been compiled together with the director of CONAPLAMED. (Annex II.)
   Average number of participants : 20 persons.

5. I paid a visit to the "Barefooted doctors" in Chinique. I gave assistance in projecting a laboratory suitable for producing tincture and granules in accordance with the GMP specifications.

6. We have organized a demonstration for private firms in the pilot plant where we have presented on the apparatus the various solid-liquid extraction technologies, the liquid-liquid extraction, vacuum distillation and the production process of essential oils.
Number of participants : about 35 persons, specialists or owners of various firms.

B. Conclusion

1. The research organization of therapeutical products prepared from medicinal plants should be built up in the following order :
   a. Ethnobotany
   b. Analysis of products of medicinal plant
   c. Pharmacology, microbiology
   d. Botany - agrotechnology
   e. Laboratory processing technology
   f. Laboratory drug manufacturing technology
   g. Clinical testing
   h. Registration
   i. Developing industrial technology (pilot plant)

   I have set forth the above organizational order, and suggested its urgent realization.

2. The four new graduated students assigned to the pilot plant (Annex III.) were instructed to the operations that can be carried out on the plant apparatus.

3. The most important task is to develop analytical methods for the products of medicinal plants and laboratory methods for the separation and purification, and to work out production processes of the medicine forms.

4. Because of the lack of quantitative analytical methods and of the required instruments the process of extracting and of the thickened extracts could not be optimized, the parameters could not be measured.

C. Recommendation

1. It is known that in the developed countries 10-15 years are required to produce new, original medicines. To my opinion 3-4 years are necessary for developing medicinal products of plant and for introducing them on the market.

2. Further assistance should be offered for developing analytical methods and for purifying the raw concentrated extracts. (Annex IX.)

3. To my knowledge the Guatemalan firms know the production of decoctions, tinctures, elixirs and syrups; lastly they have begun to acquire experiences in producing solid forms of medicines. First step is to manufacture granules and capsular preparations, and knowing this they can engage in developing pellets, tablets or dragées. On that basis I suggest further support of the medicine production technology. Making medicinal products of higher technical level can be achieved by purification of the raw extract; development of purification technologies should be begun.

4. Breaking down phase II into years is shown in a table (Annex IV.). Based on their work during several years the French "Barefooted doctors" have gained very much experience in the fields of popular therapeutics, medicinal plants and national health; their helping intention should be called on by all means (Annex V.), and their work has to be recompensed if possible.

II. TECHNICAL REPORT

A. Laboratory situation

The laboratory of the pilot plant is poorly equipped, no even qualitative thin-layer chromatograms can be made. Analytical balances, qualitative thin-layer chromatograph, reagents, solvents, UV-lamp are necessary.

B. Situation of the Pilot Plant

The equipment of the pilot plant is operative. Some safety facilities have been realized; however in Annex VIII. those ones are listed in order of importance that have to be solved urgently.

C. Solid - liquid extraction

- Tagetes lucida (Pericon)
- Matricaria chamomilla (Manzanilla)
- Psidium guajava (Guayaba)
- Chenopodium ambrosioides (Apazote)

From the medicinal plants above concentrated extracts have been produced according to the flowchart described in Annex VI., whose qualitative analysis was made in the Institute for Analysis and Plant Chemistry by Sergio Ortiz. Neither that institute possesses instruments, for instance Densitometer and Gas chromatograph. Always 5 kg ground medicinal plant were extracted based on previous laboratory tests by means of 100% ethylalcohol, being then concentrated in vacuum. Temperature of the coolers of the apparatus was 20 to 22°C, for that reason a large solvent loss appeared at distillation.

I have outlined the possibility of the already wide-spread and much less expensive spray drying. In this case extraction can be carried out with water, the filtered aqueous extract has to be thickened and with auxiliary substance sprayed and dried. The powder received contains the active agent from which in case of weak agent granules, in case of stronger active agent tablets can be prepared. It has to be noted that the aqueous extraction - thickening - spray drying is much cheaper that the present extraction with ethylalcohol, however the final product received is much more contaminated because of the ballast materials that can better be extracted with water. (Ethylalcoholic dry extract of Tagetes lucida is 8.8g from 100g dry herb, while the dried aqueous extract is 18g from 100g dry herb; the measurements were made by Sergio Ortiz.)

D. Essential oil preparation

Essential oil was prepared from two plants :

- Chenopodium ambrosioides (Apazote)
- Matricaria chamomilla (Manzanilla).

Aim of preparation was to return it back as an aromatherapeutic active substance in the granule that can be used as a medicine. Thus the essential oil lost in the course of distillation can be returned too into the extract of the medicinal plant.

E. Granule preparation

We prepared solid medicine forms (granules) with ten different composition (Annex VII.). The concentrated alcoholic extracts were dried onto powdered sugar, flavoured with tartaric acid, and aromatized with essential oil. Then with a small amount of water it was kneaded into doughy consistency, and granulated on kitchen file. In the lack of infrared lamp it was dried on air. At present, because of the very modest equipment, products with higher level cannot be prepared.

III. RECOMMENDATIONS

A. Technical section

The process technologies of analysis and purification should be urgently further developed. Only then can be expected that the parameters of the processes can be measured, and plant medicinal products of natural origin on higher technical level can be manufactured.

B. Personal section

I have taught four graduated students to operate the experimental plant, and to carry out work at optimum level, despite of the deficiencies. The young colleagues carried out their work with great diligence, and attention.

C. Technological recommendation

1. In Annex IV. I propose the principle of gradual assistance.
2. The missing equipment of safety have to be complemented immediately (Annex VIII.).
3. The responsible persons appointed by both parties should bring in harmony the work of the university departments and of LUCAM.
4. The most important task is to develop analytical methods.
5. Research of purification operations of the extract should be begun.
6. If the registration of the first medicinal plant product has happened, the development of the medicine technology (medicine forms) has to be begun.

Csaba Lőrincz

ANNEX I.

Job description :

Purpose of project : Industrial Utilization of Medicinal and Aromatic Plant Resources for the Production of Pharmaceuticals

Task :

1. Assess the preliminary laboratory results regarding processing of candidate plant species and develop schemes for pilot-scale processing.

2. Using the polyfunctional pilot plant - expected to be installed and started up - carry out pilot-scale processing test runs.

3. Develop process-technology profiles, and determine process parameters.

4. Complete technology packages for processing one or two candidate plants.

5. Conduct on site training of local personnel in all the parameters and functions of the pilot plant.

ANNEX II.

Titles of the lectures :

1. Ethnobotany and organization of the research of the medicinal plants.
2. Collection and purification of fresh plants.
3. Drying methods of the plant.
4. Types of cutting and grounding.
5. Packaging and storage of medicinal plants.
6. Sampling rules of medicinal plants.
7. Solid-liquid extraction.
8. Liquid-liquid extraction.
9. Methods of purification and separation of the active substance.
10. Methods of plant analysis. Pharmacopoeias.
11. GMP requirements, validation.
12. Medicine forms.
13. Relations of researchers, ethics, industrial interest, patents, publications.
14. Economic analysis.
15. Equipment of safety in laboratory and workshop. Environmental protection.

ANNEX III.

List of co-workers in pilot plant :

1. Bayron Baldizon
2. Carlos Cardona
3. Antonio Medrano
4. Edwin Fuentes

ANNEX IV.

Jobs of Phase II.

Year	Medicinal plant	Analytical work	Laboratory work	Pilot plant	Target	Partners	Investment	ONUDI Coordinator	USAC Coordinator
Jun-92 Jun-93	Tagetes lucida	Elaboration of analytical methods of Tagetes lucida	Elaboration of purifying methods Developmant of granules	labour contract for private firms	Registration of one medicinal product	USAC Pharmacology Microbiology Phytochemistry Pharmacognosy LUCAM	Solvents Standards Reagents Preparative thin-layer cromatography apparates Densitometer	Ing. Thierry Muller	Dra Amarillis Saravia or Dr Armando Caseres
Jun-93 Jun-94	Psidium and Smilax	Elaboration of analytical methods of two plants	Elaboration of pharmaceutical technology for ointments and capsule	Scale up of laboratory technology of Tagetes lucida to production level	Registration of two medicinal product	USAC Pharmacology Microbiology Phytochemistry Pharmacognosy LUCAM	Solvents Standards Reagents Spray driver	Ing. Thierry Muller	?
Jun-94 Jun-95	Three plants	Elaboration of analytical methods of three plants	Elaboration of pharmaceutical technology for pellets and tablets	Scale up of laboratory technology of the five plants	Registration of three medicinal product	USAC Pharmacology Microbiology Phytochemistry Pharmacognosy LUCAM	Solvents Standards Reagents Laboratory tableting machine	Ing. Thierry Muller	?

ANNEX V.

Barefooted doctors :

1. Anne Bourgey, doctor
2. Christine Masse, academy of hygiene
3. Thierry Muller, chemical engineer
4. Jean Pierre Nicolas, botanist

Address :

Casa Prodesarrollo
14003 Chinique
El Chinique
Guatemala C.A.

ANNEX VI.

Process description :

5 kg dry, ground medicinal plant

↓ 25 + 20 l 100% ethylalcohol

$2x3^{h}$ extraction with circulatory mixing at $20^{o}C$

↓

Filtration 40 l extract

↓

Concentration

in vacuum, on water bath $40^{o}C$ to 1.0 l

To 300g powdered sugar 10 ml of concentrated extract was added in several portions, homogenized fully, and for the purpose of flavouring 2g tartaric acid was added. To the so received homogeneous mixture 2 drops of the essential oil of the used herb was added, blended to homogeneous state. To the homogeneous substance so much distilled water was added that it became kneadable hard doughy consistency, granulated on a kitchen file, then dried on paper sheets. After having dried for 3 to 4 hours, packed. It was kept in brown glass, at a cool place.

It is a solid, stable medicinal product. Without any quantitative analytical method is not possible to adjust the content of effective substance to constant.

Use : in 1 cup of cold or luke water solve 1 coffee spoon under mixing.

ANNEX VII.

Granules :

1. From the extract of Tagetes lucida.
2. From the extract of Psidium guajava.
3. From the extract of Chenopodium ambrosioides.
4. From the extract of Matricaria chamomilla.
5. From the extracts of Tagetes and Psidium.
6. From the extracts of Chenopodium and Matricaria.
7. From the extracts of Tagetes and Chenopodium and Psidium.
8. From the extracts of Psidium and Matricaria and Chenopodium.
9. From the extracts of Tagetes and Matricaria and Psidium.
10. From the extracts of Tagetes and Psidium and Chenopodium and Matricaria.

ANNEX VIII.

List of the missing equipment of safety :

1. Separation from boiler (elimination of one door).
2. The exchanges of wooden doors for metal.
3. Instituting of telephone connection.
4. Building up of douches for the case of fire.
5. Coarse for extinguishing of fire.
6. Organization of education of the fire fighting.
7. Safety valve for the tank of equipment.
8. Laboratory fire-extinguisher.

ANNEX IX.

List of recommended equipment :

1. Preparative thin layer chromatography apparatus
2. Densitometer
3. Refractometer
4. Spray drier
5. UV lamps
6. IR lamps
7. Rotavapor apparatuses
8. Laboratory tableting machine
9. Microwave oven

Annex X

22 May 1992
De Silva/jbg

Backstopping Officer's Technical Comments
based on the work of Mr. C. Lorincz
US/GUA/84/282/11-01

The report describes the work carried out by the consultant and valuable recommendations for a second phase of the project. It is very urgent that the safety aspects be completed as proposed by the consultant. The other recommendations of the expert will be incorporated into the next stage of the project.

As for the requirements for registration of traditional medicines, suggested in the report we recommend the adoption of the WHO guidelines which are similar to the requirements of some EEC countries. The consultant has carried out the tasks given in the job description very effectively. The need for the quality control of the final product and the raw materials is absolutely essential and has to be a priority concern of the government.