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ASSISTANCE IN THE PRODUCTION OF PHARMACEUTICALS FROM THE THAI TRADITIONAL PHARMACOPOEIA

DP/THA/82/006

THAILAND

Technical Report: Research and Development Review*

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

Based on the work of Nitya Anand,
Expert on Medicinal Plants.

United Nations Industrial Development Organization
Vienna

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I would like to express my deep appreciation to Mrs. Sasithorn Wasuwat and the staff of the Pharmaceutical and Natural Products Research Department for the pains they took in freely providing all the information and documents that were needed for my mission. I would also like to thank Mrs. Wasuwat for making arrangements for my visit to other institutions.

I. Summary and Conclusions

The Pharmaceutical and Natural Products Research Department (PNPRD) of TISTR has been able to establish appropriate infrastructure facilities, with an effective interdisciplinary group of scientists capable of developing drugs from indigenous plant resources and technology for their production. It has useful support of the other Departments of the Institute particularly Chemical Engineering Department, the Economic Evaluation Group and the Chantuk Farm, for experimental cultivation of medicinal and aromatic plants. It has also established useful links with other Academic Institutions, Medical Research Institutes and Hospitals in Thailand (and even a few overseas Research Institutes) for specialised biological evaluation and clinical trials, and with industry, both of the private and public sector for commercialisation of products and processes developed by it.

The research and development work of the project has made satisfactory progress to achieve most of the outputs expected by its implementation; some of the more significant achievements are the commercialisation of GARLIC NATURA, spray-dried water soluble extract of Allium sativum Linn, development of PLYGESAL, an analgesic anti-inflammatory cream from Nam Man Phlai, Zingiber cassumunar essential oil, development of technology for production of refined PAPAIN from latex of Carica papaya, of SENNA products from pods and leaves of Cassia angustifolia and of an anti-venom preparation from Phakbung tha-le, Ipomea pes-caprae (L) Roth.

The development of expertise and infrastructure strengthening of PNPRD has the right perspective and is moving in the right direction, but it will need more strengthening for it to be able to: (a) carry out a wider range of preclinical studies before the drugs developed by it could be accepted by international standards; (b) generate adequate chemical engineering, process design and cost data which would be needed for technology transfer of its processes to industry for commercialisation of its products.

A Phase II for the project is recommended to consolidate the gains already made in the present project to bring to a logical conclusion the ongoing research and development projects, to strengthen the expertise in the areas mentioned above, and to move onto some new useful projects. A programme of work for the Phase II has been suggested in the report.

II. General Overview

Development of a suitable strategy for utilisation of medicinal and aromatic plants has a special importance for Thailand. A number of plants which provide useful products of established industrial use are already available in large quantity in Thailand, while many others which at present are not available can be easily cultivated in the salubrious climatic conditions provided by Thailand. Thai Traditional Remedies (TTRs) continue to be used by a large proportion of the population, but their use needs to be put on a scientific basis and coordinated for medicare programmes along with the modern drugs. The TTRs and the plants used therein are an important potential resource material for discovery of new leads and drugs for modern medicine.

This underlines the importance of the project under review, the "Assistance in the Production of Pharmaceuticals from the Thai Traditional Pharmacopoeia", at the Pharmaceutical and Natural Products Research Department (PNPRD) of the Thai Institute of Science and Technology Research (TISTR). This project was originally submitted to the UNIDO in 1981. A consultant was fielded by UNIDO in 1982 to review, among other things, this proposal for technical assistance by UNIDO. The present revised version of the project was submitted in consultation with the consultant in December 1982. The project was approved by UNIDO in August 1983, and by the Government of Thailand in January 1984; the project was initiated in June 1984.

The objective of the present mission were: "To evaluate the research and development results after two years of research and development activity. The consultant will also participate in drawing up the "forward lists" of substances to be investigated and/or developed by TISTR in the future."

(a) Staff: The staff provided for this project from the Thai Government funds has been recruited and is in position, except for the Chemical Engineer; this post has also been advertised but no suitable candidate could be found, due apparently to shortage of chemical engineers. It

is suggested that a bright M.Sc. or Ph.D. (Organic Chemistry) may be recruited and deputed to work in a Chemical Engineering Laboratory, or in industry for practical training in process development and unit operations. The staff of PNPRD has thus been substantially increased since the beginning of this project (Annex 1).

(b) Equipment: Except for the 500 lit. Glass-lined Percolator and the Vacuum Drum Drier, all the other equipment sanctioned in the project has been procured and is in operation (Annex 2). The percolators have also been ordered, and are expected by the end of November 1985. There has been some difficulty in identifying suitable suppliers for the Drum Drier, and also considerably low estimation of the cost. A supplier of Vacuum Drum Drier has now been located, but the price quoted is US$53,000.00 instead of US$10,000.00 provided in the budget. Vacuum Drum Drier would be useful for preparation of dry solid/powder from water extract of plants, and effort should be made to provide extra funds for it, either by re-appropriation from other heads or by approaching another source; simultaneously alternative suppliers who may be cheaper should also be explored.

During this period some equipment has been received from other sources as well, such as a Multi-purpose Extractor received as a gift from Italian-Thai Holding Company. All these are also included in Table II.

(c) Building: There has been an acute shortage of space in the PNPRD. To partly overcome this limitation, a separate building of about 300m^2 was provided for in the project for the Pharmacology Section. The construction of this building, though approved in principle, was considerably delayed, due to various administrative reasons, which has been a bottleneck in the efficient running of the project. The building is now completed and is being furnished and occupied.

(d) Training: Nine man-months for three trainees, one each in Quality Control, Pharmacological Screening and Chemical Technology were provided.

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The first two have been completed, while the third was delayed because of the delay in recruitment of a Chemical Engineer/Chemical Technologist. The third trainee has also now been identified, the training deputation approved, the host institution informed and the training will commence in early 1986. The training slots would thus be fully utilised and in good time.

I had a discussion with the trainees about their training. While the training of the Pharmacologist seemed to have gone off well, the training of the Analytical Chemist in Quality Control Methods did not seem entirely satisfying. She felt that she did not learn as many new things as she would have liked to. It would appear that with a little better planning, more mileage could be gotten out of the training programme. A detailed letter from the Project Director to the Head of the host laboratory, giving the relationship of the training to the objective of the project, and outlining the specific techniques or procedures in which training is required would be desirable. The host institution would then be better prepared to receive the trainee and could arrange for the specific training required. The training arrangements should not be left at a very formal level but should form a very organic link between the host institution, the Project Director, the trainee and the project objective.

(e) Study Tour: The Project Director, Mrs. Sasithorn Wasuwat undertook a study tour of one month as scheduled, and visited some laboratories working on the development of plant products in Sweden, United Kingdom, West Germany, Switzerland, Romania, Bulgaria and China. She appears to have had fruitful discussions, made useful contacts, and established the possibilities of joint collaborative research projects with laboratories in China and Sweden.

(f) Expert Visits: Four expert visits have been provided for a total of 12 man-months, six for Pharmacologist, four for Chemical Technologist and one each for Marketing and Medicinal Plants. The Marketing Expert, Dr. J.G. Meredith, visited Bangkok from 13 June to 6 July 1985 and has already submitted his report. The Pharmacology Expert, Dr. F. Sandberg visited PNPRD from August 1984 to January 1985, October to November 1985 and is expected back for one week in March 1986. The Medicinal Plant Expert mission, meant mainly for evaluation, was started on 3 November and will be completed on 2 December 1985. The Chemical Technology Expert will come in March 1986.

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There has been some shifting around in the timing of the visits of the experts from what was originally planned, which has not been ideal for the project.

My visit, meant mainly for evaluation and identification of future projects, was supposed to take place after two years of the running of the project, but has taken place when the project has been running only for one year and four months. The Marketing Expert's visit was supposed to take place simultaneously with or following soon after the Medicinal Plants Expert's visit, so that the advice of the Marketing Expert could be sought for the products identified by the Medicinal Plants Expert, and the work of the two could be coordinated. Luckily Dr. Meredith and I were visiting Vienna at the same time before his visit to Bangkok, and could discuss the project document, and so Dr. Meredith had the input of my views before undertaking his mission.

The Biology/Pharmacology Sections have been acutely short of space, and would have been fully operational only after the new building was fully ready. It would have been more useful if the Pharmacology Expert, Prof. Sandberg, had visited after the new building was constructed and fully operational, so that he had to spend his time in only training staff and transferring expertise in pharmacology experiments. His first visit was long before the building was completed, and the second when the building was just completed and getting furnished. Prof. Sandberg kept himself usefully and fully occupied and helped the staff in various ways; Prof. Sandberg is a very senior and highly reputed Pharmacologist, and much more could have been gotten out of his mission with better timing.

Much of the problem has arisen because of the delay in receiving the formal sanction of the project from the Thai Government, and of the delay in the construction of the pharmacology building, both of which were beyond the control of the authorities concerned with the running of the project. It is difficult for the experts to reschedule their visits at short notice.

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The Chemical Technologist, Mr. Sugar, is due in 1986. His expertise is needed mainly for upscaling and process design, and his coming late in the project would be more useful, when laboratory processes for most of the products under study have been developed, so that his advice could be sought for all the projects. His visit for four months in March to June 1986 or even a bit later is in perfect order.

(g) Progress Reports: Four progress reports for the periods February 1984, August 1984, February 1985 and July 1985 were required to be submitted by the Project Director. Three reports covering the periods from 1 August 1983 to 31 January 1984, February to July 1984 and August to December 1984 have been submitted. The fourth report covering the period from 15 December 1984 was due in July 1985. The report is almost ready and will be submitted in the first week of December 1985.

The first tripartite review, originally planned for September 1984, was held in January 1985.

(h) Publications: A number of internal technical reports, and Handbooks for the cultivators have been published by PNPRD, which do show the large volume of research and development work carried out by the Department. However, rather few scientific research papers have been published. It is true that work essentially of an applied nature may not lend itself easily to original scientific research papers, and patents should be filed for the work. Further in all research, whether pure or developmental, there is an element of innovation and it is only this that keeps a scientist motivated to do research, and there are a number of journals now adays which will publish papers with an applied bias. Apart from scientific recognitions, publication of research papers has many other aspects too; the work gets refereed by peers in the field and useful new ideas are often received from the referees; the work gets thrown open for scientific community's scrutiny; while writing a scientific paper requires a lot of discipline, scientific rigour and order is brought into the work. So I would urge the Project Director to attach due importance to original scientific publications, which will provide incentive and motivation to scientists for more and better work.

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(i) Scientific Meetings and Seminars: Now the strength of the staff in the PNPRD is increasing and new, young bright scientists are being recruited, it is important to give attention to raise and maintain the scientific level of the staff at a high level. It would be useful to organise regular fortnightly/monthly seminars in the Department, both for literature survey as also on topics of current research interest, and to regularly invite guest lectures from other institutions.

III. Review of the Research and Development Programmes

The review of the research and development programmes and of the achievement of different objectives given below is itemised according to the project document.

A. Development Objective

To promote the utilisation of Thailand's resources of medicinal and aromatic plants thereby enhancing self-reliance in the field of pharmaceuticals while providing income to agricultural producers of the plant material.

In the context of the present project, there are two main uses of the resources: (1) to make drugs and chemicals of proven economic value (drugs of modern system of medicine) for which plants are either available in Thailand, or can be easily cultivated; and (2) their use as drugs based on the Thai traditional pharmacopoeia. To promote their use for the former, it is required to develop industrial processes for their production, while for the latter it is required to scientifically verify the claims for the Thai Pharmacopoeia and for some products used commonly as household remedies by pharmacological investigations and formulate these into acceptable pharmaceutical forms, develop standards for quality control which would greatly increase their acceptance as drugs. Research is thus needed at three distinct levels: (a) for development of processes for industrial production; (b) pharmacological investigation; and (c) development of new pharmaceutical formulations and quality control standards/methods for the products identified in (b) above.

With the support of the UNIDO project, it has been possible for the PNPRD to strengthen its capability and expertise in these three areas.

For the utilisation of the research and development results, there is need to establish liaison with the user agencies, be they in the private sector or in the public sector. The PNPRD/TISTR has been able to establish some channels of liaison with the domestic industry which has helped in the utilisation of the research and development outputs. These channels would, of course, need to be continually strengthened and enlarged. It is

10/suggested

suggested that a joint Consultation Committee be formed by TISTR/PNPRD with representatives of the industry, to inform the industry of research and development results and for the industry to get an opportunity to suggest any problems in which they may be interested. An annual get-together with the representatives of the industry may be another way of increasing contact with them.

There is a growing world interest and demand for herbal products and of drugs of the traditional systems of medicine, and this has resulted in an increase in trade of raw drugs in the world market. There is a certain amount of export of raw drugs from Thailand. There is a distinct possibility of greatly increasing the export of the crude drugs by standardising and improving their quality, as also some of drugs of the traditional pharmacopoeia. Preliminary contacts have been made with some commercial/industrial houses in countries abroad, including in developed countries for export of some of the products developed by PNPRD/TISTR. These contacts, however, need to be strengthened and expanded. A useful suggestion has been made by the Marketing Expert to establish marketing research operation within the Economic Evaluation Group of TISTR, which should be followed up.

B. Immediate Objectives

1. To develop the production technology at pilot scale of selected products of established economic value.
2. To document the technical and economic feasibility of the recommended processes with regard to the local and the export market.

Technology has been developed for: (1) production of senna extract, senna tablets and senna tea; and (2) for the production of pro-tincture of ginger.

3. To optimise the quality of a few plants of the Thai traditional pharmacopoeia to meet the rigid specifications required for export.

Technology has been developed for preparing light colour rhizome slices of Zingiber officinale for export and the report transferred to

the Thai Commodity Company. Conditions for cultivation, period of collection and storage of senna leaves and pods to maintain good quality have also been determined. Suitable booklets on the agricultural and post-harvest practices to assure good quality for these two plants are under preparation and would be ready for distribution by June 1985.

4. To develop suitable formulations for a few drugs derived from plants and remedies of the Thai traditional pharmacopoeia for their eventual use in medicare programmes.

A major achievement has been the development of a suitable formulation of garlic (Garlic Natura) which is being marketed by Natural Products Industry, a privately owned company. Pharmaceutical formulations have also been developed for an anti-inflammatory agent from Z. cassumunar named Plygesal, and a limited clinical trial carried out which is indicative of its effectiveness. This is ready for commercial exploitation and industry is being contacted for this purpose. An anti-venom cream has been prepared from Ipomea pes-caprae for use against jelly fish stings and a limited clinical trial carried out which is showing promise.

5. To inform the local pharmaceutical industry, generate interest in undertaking production of the products developed and provide assistance in production technology and marketing.

A meeting is held with the Government Pharmaceutical Organisation (GPO) every month to inform them of the research results of PNPRD/TISTR. The private industry is advised of the results through the Research News Bulletin of TISTR, and TV and newspapers coverage through the Ministry of Science and Technology. The private industry is also encouraged to contact the Director of PNPRD to know of the research results and for personal discussions.

6. To train the staff of TISTR in the pilot manufacturing process and quality control procedures involved.

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The staff of TISTR has been trained abroad under the fellowship and visit programmes of this project and Annex 1 gives details of the staff thus trained.

C. Review of Outputs

1.1(a) Senna products

Technology has been developed for the preparation of senna concentrate from pods and leaves of Cassia angustifolia containing 20 - 25 per cent of calcium sennosides. This process has been standardised in the pilot plant up to 10 Kg. batch size. Some indicative costing of this process has also been worked out. Processes have been developed for the preparation of senna tablets from ground senna leaves, pods and senna concentrate, and for senna tea. Method has been standardised for determining sennosides content in each product. The process for manufacturing tablets from leaves and pods have been demonstrated and transferred to the Government Pharmaceutical Organisation (GPO). It is likely that they would also take up the production of senna tea. The private industry has shown interest in marketing of senna tea.

So far the GPO has not shown interest to market the tablets made from senna extract. It may be useful to establish contact with the private industry to market senna tablets made from extract. There is a world demand for senna extract and sennoside tablets. However, the main requirement in the European market is for senna extract with more than 40 per cent of calcium sennosides content or of pure sennosides.

Recommendation

1. Private industry should be contacted to utilise the technology developed for the production of senna extract and sennoside tablets; tablets containing senna extract would be more acceptable in the market.

2. Efforts should be made to export senna products particularly to Europe, the USSR and the Eastern bloc countries where there is a good

13/demand

demand for senna products. For this it would be necessary to upgrade the senna concentrate to higher proportion of calcium sennosides, at least about 40 per cent.

1.1(b) Pro-tincture of Ginger

A process has been standardised on a semi-pilot scale for the preparation of pro-tincture of ginger having 8 per cent solid content. Suitable quality standards have been developed for this protincture. Industrial outlet is being explored.

Recommendation

Suitable upscaling of this process should be carried out.

1.2 Papain

Technology has been developed for the production of refined papain from papaya latex with proteolytic activity of over 1700 i.u/gram. This process has been standardised on a pilot plant batch size of 10 Kg. of latex giving about 1.0 Kg. of papain of the above grade. The PNPRD is in touch with the industry for commercialisation of this product. A feasibility report has been prepared.

Chymopapain is another useful enzyme which can be prepared from C. papaya latex. It is considered to be the product of choice for herniated disk treatment. Now that research on development of a process for production of papain is progressing satisfactorily, it would be useful to explore the possibility of simultaneously producing chymopapain which will add to the economic viability of the project.

Recommendation

1. For export, the cost and quality of papain are of great consequence because of strong commercial competition in this field. It is therefore important to devote more time to improve the economics of the process. The idea of a composite papaya fruit based industry with proteolytic enzymes as one of its range of products should be promoted.

2. Work should be initiated to produce chymopapain from papaya latex.

1.3 Bromelain

In view of the fact that a senior staff member of the Department of Chemical Engineering of Chulalongkorn University has decided to work on this project, and there were other pressing demands on the staff of PNPRD, the PNPRD did not start work on this project. I would not agree to this view. In view of the availability of very large quantities of pineapple waste in Thailand and good commercial demand for Bromelain, even two laboratory working on the development of technology for Bromelain currently and for utilisation of other products available from the waste such as wax is justified. The two laboratories should concert with each other and exchange the results so that a more expeditious development of technology can take place.

Recommendation

PNPRD should take the development of technology for Bromelain and wax.

1.4 Nicotine

A number of samples (about 10) of Virginia type tobacco waste from different regions in Thailand have been analysed and found to be very poor in nicotine content ($< 1\%$). It was, therefore, decided to drop this project. During a visit to one of the large Thai tobacco producing companies, it was found that Burley type is the second largely cultivated type of tobacco in Thailand and about 3500 tons of leaf waste of this type would be available annually. According to the information available the leaves of Burley type would have about 3 per cent nicotine content.

Recommendation

The Burley type tobacco leaf waste from different regions of Thailand should be analysed, and if found to contain around 3 per cent nicotine, technology for its production on pilot plant scale should be developed.

1.5 Utilisation of sugarcane press mud

It was not possible to start this project due to other pressing demands and it is intended to initiate work on it in 1986.

Recommendation

In view of the large availability of sugarcane press mud and possibility of making a number of products of economic value from this agricultural waste, this project should get priority in the future work.

1.6 Vit. E concentrate from rice bran oil

Some preliminary work has been carried out on rice bran oil to prepare fractions rich in Vit. E (0.3% Vit. E content). More work, however, needs to be done to increase the Vit. E content so that the product could be used as Vit. E supplement. A new useful dimension has been added to this project by exploring the simultaneous production of oryzanol from rice bran oil, which is used in cosmetic industry and as a pharmaceutical product.

Recommendation

1. Further work should be carried out to obtain fractions with higher Vit. E content, the process upscaled and techno-economics worked out for production of Vit. E concentrate and oryzanol.

2. A number of industrial products apart from Vit. E concentrate, oryzanol and edible oil can be prepared from rice bran which is an agricultural waste, which include industrial board, cement from the ash and charcoal. Therefore, if the production of the rice bran oil could be made into a composite rice-bran based industry, it would greatly add to the economic value of this project. TISTR is ideally bared to be able to undertake such a project because it has the department required to undertake other aspects of this project. It would be useful to consider this project being made a part of one of the Institutional Projects of TISTR.

1.7 Lime Oil

There has been very poor lime crop in the last two years and limes at economic prices were not available and therefore this work could not be initiated.

Recommendation

Lime oil has good international market. Therefore, as soon as a good lime crop is available, it would be useful to undertake this project and develop technology for the production of lime oil conforming to export quality standards.

1.8 Zingiber officinale pro-tincture

A laboratory process has been developed for the production of pro-tincture of ginger with 8 per cent solid content which would be useful for galenical preparations. The Medical Department, Royal Thai Air Force, is interested in this product and is likely to take this process. The private industry is also being contacted.

Recommendation

This process should be upscaled and techno-economics of the process worked out and a feasibility report prepared.

1.9 Amomum xanthoides oleoresin and pro-tincture

As pro-tincture maintains the top-note better than the oleoresin, some preliminary work has been carried out for the preparation of both the pro-tincture and the oleoresin from A. xanthoides. More work is needed to optimise these technologies.

Recommendation

The process should be upscaled, the techno-economics worked out and a feasibility report prepared.

2. Improved Standard/Quality Plant Materials for Export

Technology has been standardised for keeping light colour for slices of Z. officinale needed for export, and the technical report transferred to the Thai Commodity Company, who have already commercialised this technology.

Revised editions of the Handbooks for preparing good quality rhizomes of Z. officinale and Curcuma longa are under preparation.

Recommendation

The development of optimal conditions for collection, drying and storage of rhizomes of C. longa, Z. officinale and fruits of Amomum xanthoides from different regions of Thailand should be completed soon and information transferred to concerned organisations and revised Handbooks then prepared.

3. Development of Drugs

3.1 Zingiber cassumunar

Phlai oil, the essential oil obtained from the rhizomes of Z. cassumunar was found to possess analgesic-anti-inflammatory and spermicidal activities. Detailed evaluation and preclinical studies have shown its promise as candidate drug for both these activities.

3.1.1 Plygesal, an anti-inflammatory cream

After a limited clinical trial for analgesic-anti-inflammatory activity, a cream preparedfrom phlai oil is now ready for marketing. Industry has been approached for contract of this product.

The clinical trial so far carried out had only eight patients and was not sufficiently controlled. It was indicative of satisfactory pain relieving effect of the preparation which is a very subjective criteria. It would now be useful to carry out detailed pharmaceutical tests to have a more quantitative assessment of the anti-inflammatory and analgesic activity. The clinical trial should also be enlarged to include more objective criteria for assessment of the efficacy of the products. These studies, however, should not preclude the marketing of the product as there seems to be good acceptability and lack of any toxicity.

Recommendation

1. A quality control method for the cream such as GLC finger print standard should be developed.

18/2.

2. Concurrent with the marketing of the product, studies on the mode of action and a larger clinical trial should be continued.

3. When the product is marketed, a mechanism should be developed for post-marketing surveillance for product acceptability, efficacy, side-effects and formulation improvement, and with the feedback thus received, the products acceptability may be enhanced.

3.1.2 A spermicide from phlai oil

By fractionation of the oil, the spermicidal activity was found to be concentrated in one fraction which has been characterised as terpinen-4-ol. This is a new structural lead for spermicidal activity and an important contribution from this work. A short-term preclinical toxicology study has been carried out with this active fraction prepared into a cream. More preclinical and clinical work would now be needed to develop a suitable formulation either from this fraction or from pure terpinen-4-ol depending upon the economic availability of either of these products.

Recommendation

1. The identification of terpinen-4-ol as the spermicidal agent in Z. cassumunar is an important development and should be fully exploited. Preclinical toxicology and clinical development of terpinen-4-ol as a spermicide should be carried out expeditiously. As this would involve a considerable amount of cost and coordination, it would be useful to explore collaboration with industry, whether of the private or the public sector, at this stage. This would help to give the work greater speed.

2. The uncovering of the spermicidal activity in terpinen-4-ol is an important structural lead. It would be useful to consider filing a use-patent for this product. It is also suggested that structure activity relationship studies be carried out based on this structural lead to explore the possibility of developing even more effective spermicides.

3.2 An anti-venom preparation from Ipomea pes-caprae

Based on an observation made earlier in this laboratory of anti-jelly fish venom activity, a clinical trial has now been carried out with

a cream prepared from an aqueous extract prepared from this plant against stings of jelly fish,which has shown promising results. This could be very useful for fishermen living in the coastal areas and for people going for swimming in the ocean infested with this fish. Large-scale preparation of this cream for preclinical and clinical developmental work is under way. Some work has been carried out on the chemical isolation and characterisation of the active principle,but it has not yet been possible to purify it to a state of homogeneity. Joint scientific collaboration has been started between PNPRD and the Department of Pharmacognosy,, School of Pharmacy, University of Uppsala, Sweden, for chemical characterisation of the active constituent, and this shou..d help to enhance the speed of the work.

Recommendation

This is a project of great public health importance. As the ipomea preparation appears to have a very specific activity, it would be of great scientific interest and importance to characterise the active constituent of the plant. The large-scale availability of the plant is also in doubt, and therefore the chemical characterisation of active material may make it possible to synthesise the product to make it more easily available. It is therefore suggested that while clinical development work may go on with the extract, simultaneous work on the characterisation of the active principle should be pursued expeditiously.

3.3 Anti-cancer and anti-amoebic preparation from Brucea amarissima berries

It was shown earlier that the aqueous fraction of the plant,which is free of bruceantine, and has rather low acute toxicity,had in vitro anti-cancer activity against KB cell line and in vitro anti-amoebic activity. During the present period of this project, both these activities have been confirmed and not much further progress could be made, due to difficulties for arranging for in vivo testing for these activities. Some effort has been made to procure special inbred strains of mice and cancer cell lines needed for producing tumours in experimental animals.

Recommendation

1. Testing for anti-cancer activity is a very specialised and costly affair. It will not be fruitful for TISTR to undertake the testing for anti-cancer activity. The facilities available at the National Cancer Institute,

20/Bangkok,

Bangkok, for preliminary anti-cancer screening should be utilised; they had earlier identified the anti-cancer activity in the aqueous extract of Brucea amarissima. The non-aqueous fraction of this plant is known to contain bruceantine, a quassinoid with high anti-cancer activity, but its usefulness is limited because of its high toxicity. If, therefore, a non-bruceantine fraction with low toxicity is found to possess anti-cancer activity, it would be a very important development. The National Cancer Institute (NCI), NIH, Bethesda, MD, USA, has carried out the entire testing and development work on bruceantine as an anti-cancer agent. The NCI carries out anti-cancer testing of products received from all parts of the world and has indeed the most comprehensive anti-cancer screening programme in the world. Therefore, rather than to try to set up comprehensive anti-cancer testing at the National Cancer Institute in Bangkok, it is suggested that the extract, after preliminary testing, be sent to the NCI, USA, to test anti-cancer activity against a range of animal tumours, and to compare the activity with other known anti-cancer agents to fully assess its potential activity and usefulness. If found promising, this lead should then be followed with the utmost priority. Similarly, the anti-amoebic activity of this product should also be assessed in a laboratory which is routinely carrying out in vivo tests for anti-amoebic activity. Only when in vivo activity is confirmed should any further work be carried out.

2. Bruceantine is a well-recognised bio-active substance. When large quantities of brucea berries are being processed to get the above water soluble fraction, it would be useful to simultaneously prepare bruceantine; there would be a small but definite economic outlet for this product.

3.4 Azadirachta indica

Not much progress seems to have been made during this period on this extract, except confirming the in vivo anti-malarial activity, including against chloroquine resistant strains of P. falciparum. Definitive in vivo anti-malarial activity should be confirmed before any further work is planned on this plant.

21/Recommendation

Recommendation

Any further work on this extract should be carried out only after in vivo activity has been confirmed.

3.5 Some more plants for drug development have been identified for further work and are given under proposed Phase II of the project.

3.6 Garlic formulation

Garlic has been a food and a household remedy for a variety of ailment in most of the old civilisations, and its use has continued to modern times. Its medical use is now settling down on a more scientific basis with the demonstration in recent years of CVS effects of various preparations of garlic, including lipid lowering and anti-thrombotic activity. In view of its strong odour, a suitable formulation which is easy to administer is of great interest. In this context the development of spray dried garlic extract in capsule form in the present work, with demonstrated hypolipidemic activity in experimental animals and also clinical efficacy, is an important achievement. It is gratifying that Natural Products Industry, a private company has put up a plant for this product and will commercialise it under the name "GARLIC NATURA". It was very satisfying to visit this plant, set up under the consultancy of PNPRD. The plant is observing very good GMP and can compare favourably with any such plant set up in any highly developed country, and the NPI seemed to be very satisfied with the consultancy provided by PNPRD. According to the consultancy agreement PNPRD will keep a check on the quality of the product. This plant processes 500 Kg. of cleaned garlic bulbs (obtained from about 750 Kg. of bulbs obtained from the market) per shift of 12 hour, and can thus process 1.5 tons of garlic in one day, which is obtained from 3 rai of land. This consumption of garlic would thus provide an income of ฿75,000.00 per day for the farmers.

A recent development in thisfield has been the preparation of deodorised garlic powder. The PNPRD has been able to develop a process for this preparation. It would be useful to test the biological activity of this preparation.

22/Recommendation

Recommendation

1. A post-marketing surveillance and monitoring of "Garlic Natura" should be organised to get a feedback on the field use of this product.

2. Detailed biological studies with this product, as also with deodorised garlic powder, should be continued to study the mode of action, as also to find out if the action is due to specific chemical entity.

3. The quality control standards developed so far include standards for only moisture, total protein and sugar content. It would be useful to add some test for chemical constituent characterisation, such as a GLC finger print, and/or infrared/U.V. spectrometery; controllable standards are crucial for promoting plant products of this type. The work already being initiated on the GLC/HPLC analysis of this product should be expedited, and its re-producibility checked on the different types of garlic, samples available in Thailand.

4. Industrial Extension

Three of the products developed by the PNPRD have been commercialised by the industry which include "Garlic Natura" by Natural Products Industry, Senna Tablets by GPO and Z. officinale slices by the Thai Commodity Company.

Programme of Work from December 1985 to September 1986

This programme has been drawn up in consultation with Prof. F. Sandberg, Expert in Pharmacology and Mrs. Sasithorn Wasuwat, Project Director.

1. Production Technology at Pilot Scale

1.1 Senna products

(i) Optimise the extraction of sennosides from leaves and pods.

(ii) Prepare senna extract with > 20% and nearing at least 40% calcium sennoside content.

(iii) Develop a HPLC method for quantitative estimation of sennosides.

(iv) Development of any special senna formulation referred to by the industry.

1.2 Papain

(i) Undertake development of a process for production of chymopapain from latex of papaya.

(ii) Upscaling of production of papain to about 50 Kg. of latex per batch.

(iii) Prepare detailed feasibility report for a composite papaya based industry which should include the enzyme preparations as one of its range of products.

1.3 Nicotine

The Burley type tobacco waste sample from different regions of Thailand should be analysed for nicotine content, and if found to contain > 3% content, the process for production should be upscaled to pilot plant scale.

1.4 Products from sugarcane press mud

This work should be started as soon as possible.

1.5 Vit. E concentrate

The laboratory work already started should be upscaled to prepare pure oryzanol and Vit. E concentrate with higher vitamin content.

1.6 Z. officinale and A. xanthoides pro-tincture

The laboratory processes should be upscaled and techno-economic feasibility reports prepared.

2. The revised/new Handbooks on various plants identified in Project Document describing practices for cultivation, harvesting, storing and transportation should be finalised soon, and in no case, later than June 1986.

24/3.

3. Development of Drugs

3.1 Zingiber cassumunar oil as spermicide

Preclinical development of terpinen-4-ol: carry out development of a formulation, sub-acute toxicity in two species of animals mutagenic and teratogenic studies.

Concurrent with the marketing of Plygesal, further work should be continued on studying its mode of action and clinical efficacy.

3.2 Anti-venom cream from Ipomea pes-caprae

Clinical characterisation of the active principle should be pursued, along with some preclinical development studies with the cream already prepared.

3.3 Anti-cancer and anti-amoebic products from Brucea amarissima and

3.4 Anti-malarial product from Azadirachta indica

Sufficient quantities of B. amarissima extract sent at an early date to Dr.C.V. Naraynan, National Cancer Institute, NIH, Bethesda, MD, USA, for in vivo anti-cancer screening against a panel of animal tumours. B. amarissima and A. indica extracts should be sent to Tropical Disease Institute, Bangkok, for in vivo anti-amoebic and anti-malarial screening respectively. Further development of these products as drugs should be carried out after these in vivo testing results are available and are properly evaluated.

3.5 Garlic products

(i) Quality control criteria for Garlic Natura should be enlarged to include chemical composition as one of its standards.

(ii) Work on odourless garlic preparation should be upscaled.

IV. Critique

Investigation and utilisation of plants and traditional remedies have both scientific and economic dimensions. Cultivation and collection of medicinal plants provides means of livelihood and/or added income to a sizeable proportion of people living on the land. Most of the traditional remedies are made from plants and a large segment of the population still depends upon these remedies for their medicare needs. It is therefore important to put their usage on a more scientific footing by standardising and modernising their production, by developing quality control standards for them and by scientifically verifying the claims made for their activity. Plants continue to be the only economic source for a number of well-established modern drugs and important chemicals, and their indigenous production would be of national economic gain. There is a growing world trend, even in developed countries, towards greater use of herbal drugs and traditional system remedies, and the demand of raw drugs in the international market is increasing. To get raw drugs of assured quality for export, it is important to control quality of cultivation, standardise the period and conditions of harvesting, storage and transport and advise the farmers on these points. Plant products have been the most important resource not only for the development of new drugs, but what is even more important of new leads for molecular modification to new drugs, and modern drug research has drawn heavily on such leads. The objectives of the present project document reflect an appreciation of the importance of these different dimensions of the research on plants and traditional remedies and the work plan is grouped under these different heads as t oproach to investigation in each area is distinct somewhat from the other s has also made it easier for each task to be followed and monitored separately.

To achieve the objectives set here-in-above, an inter-disciplinary group of scientists, consisting of chemical technologists, organic chemists, pharmacists and pharmacologists, would be required to work together. Such a group would in turn need to coordinate its work with the hospitals for clinical trials on one end and with industry on the other for utilisation of its results.

26/Though

Though even before the UNIDO support for this project became available, nucleus of an inter-disciplinary group was available at the PNPRD, but it was rather small to be effective, and deficient in some important areas such as chemical technology, phytochemistry/medicinal chemistry and biology/pharmacology. The UNIDO support has helped to strengthen the group in some of these deficient areas both in staff and equipment, and there is now a good inter-disciplinary group working under one roof in a mutually interactive manner. Though some further strengthening in chemical engineering/technology, phytochemistry and preclinical toxicology studies would be needed for the Department to become fully effective, the group on the whole can work in a well coordinated and coherent fashion, and is now set to take on bigger tasks for utilisation of plants and natural products as drugs and aromatic chemicals. Thus, a good scientific foundation seems to be getting established. This would appear to be the biggest achievement of the project, and would help in fulfilling the Development Objectives set for the project.

It is gratifying to note that satisfactory progress has been made in practically all the Immediate Objectives set for the project, as is evident from the review given above of the progress of work of the project. Among the more significant achievements are:

(1) Standardisation of a suitable formulation for garlic, "Garlic Natura", based on widespread tradition of medicinal use of garlic, which is already in commercial production; the farmers will benefit from greater consumption of garlic bulbs;

(2) Processes for production of senna extract (20 - 25% calcium sennosides content) tablets and tea; technology for production of tablets made from senna leaves and pods has been passed on to the Government Pharmaceutical Organisation, and of senna tea to a private industry, who are likely to start production of these senna products based on this technology;

(3) Development of an anti-inflammatory cream from Z. cassumunar for topical application;

(4) Development of a spermicide from Z. cassumunar, and its characterisation as terpinen-4-ol, which is a new and important structural lead for spermicidal activity, and may open up a new area for developing new spermicides;

(5) Development of an anti-venom preparation from Ipomea pes-caprae against jelly fish sting, based on folklore use of this plant; this would have public health use;

(6) Process for production of high quality papain from Carica papaya latex.

The work carried out in the project has thus on the whole contributed to fulfilling the scientific, technological and economic expectations, and satisfactorily achieved the immediate and development objectives set for it.

The special strengths of the project group of PNPRD are: (1) a highly motivated and dedicated Project Director, who also enjoys high respect and prestige in scientific and industrial spheres in Thailand, which has greatly helped the project to achieve what it has done requiring a great deal of inter-institutional coordination in work and also commercial utilisation of the outputs of work; (2) a well adjusted good inter-disciplinary group of scientists in PNPRD, with good atmosphere and discipline for work; (3) special expertise in the Department in the area of biopharmaceutics and formulation development; (4) a good institutional frame work of TISTR with other scientific departments to support its activities, and particularly of Chemical Engineering Group, Workshop, Documentation Centre, Economic Evaluation Group and Agricultural Farm.

Some of the weaknesses of the project/group have been: (1) insufficient emphasis on process design and techno-economic data needed for industrial production of products; (2) lack of sufficient expertise in phytochemistry; (3) the biological activity interests are spread over a rather broad area, and the resulting difficulty in developing special expertise in so many areas; (4) lack of expertise in preclinical toxicology studies; and (5) lack of sufficient expertise in clinical pharmacology studies, resulting in getting clinical data which is not sufficiently controlled and quantitative for an objective assessment of the efficacy of products under development.

A general difficulty that the project faces is the rather weak base of indigenous pharmaceutical production in Thailand and lack of Governmental support and incentives to encourage indigenous production, resulting in few buyers/customers for purchase of technology and very few pharmaceutical industry sponsors to support projects for development of technology. A favourable feature is a great deal of interest in the people in drugs of Thai pharmacopoeia and in utilisation of plant resources in general, which creates a favourable climate for utilisation of results of this project. Thus, the project's importance, achievements and problems have to be viewed in the background and appreciation of all these issues.

There has been a general overall growth of PNPRD in all its spheres of activity during the period of this project. Its range of expertise has widened in scope and infrastructure facilities greatly increased. It is gradually emerging as an important centre for research and development on plant products. The visit of Mr. Sugar, the Expert on Chemical Technology, should help to get greater expertise in the area of process design and generation of techno-economic data.

There has been addition of some very well-qualified staff in the area of organic chemistry during this period which should help in strengthening the phytochemical component of the project. Though it may not be necessary to characterise chemically the active constituent in every product being developed as a drug, but for the scientific growth of the project, it would be useful to know the structure of the active constituent. Therefore, a high level of phytochemistry should form an integral and important part of this project. With the new staff added this gap would be to some extent filled.

The PNPRD is aware of the need to build a strength in the area of preclinical toxicology and is gradually trying to build expertise in this area. In the coming years, it should thus be possible to take remedial steps to strengthen the project in the spheres in which it is rather deficient.

It would greatly benefit the PNPRD and help it to fulfil the development objectives of the project more effectively if the project support could be continued for another period of three years; a programme of work and an indicative budget for the second phase of the project has been suggested.

V. Future Prospects

Project of this nature dealing with development of new drugs from plants and traditional remedies and of technology for their production needs the establishment of an inter-disciplinary group. To establish such a group with expertise of different disciplines would take time, and a period of less than two years is too short a period to expect a fully effective and operational group of this kind to be established. All that one can judge is whether the group is developing in the right direction and getting the right expertise and support, and from some demonstrable outputs, judge its long-term potential and whether it would be able to achieve the development objectives set for the project. The PNPRD has been conceived as an inter-disciplinary group; it has the right perspective; it has the right leadership in Mrs. Sasithorn Wasuwat; it has the support and back-up of a big multi-disciplinary institute in TISTR. PNPRD is recognised by the Government circles such as the National Economic and Social Development Board as a major centre for work on medicinal and aromatic plant. It has established good inter-institutional links with academic institutions such as the Schools of Pharmacy and Hospitals and Chemistry and Chemical Engineering Departments of different universities who are represented on the Steering Committee of PNPRD. It has also good rapport with the pharmaceutical industry, both of the private and public sectors. The PNPRD has thus the right ingredients for playing a useful role in developing into a major centre for industrial research and development work for promoting the utilisation of plants and traditional remedies in Thailand.

The support given by UNIDO to the present project has greatly helped PNPRD to strengthen its infrastructure facilities and develop expertise in the areas of pharmacology and pharmaceutical analysis. However, there are still some gaps in its expertise for it to carry out the whole range of studies needed for new drug development in the modern context, such as for preclinical toxicity studies and some specialised immunological studies. It also has some deficiencies in its expertise in the area of chemical technology, process and project design for commercialisation of its processes. If support could be provided for the second phase of the

31/project,

project, this would help the project to consolidate its present gains and fill the gaps and deficiencies which exist, and thus establish a strong foundation of an inter-disciplinary group. This would then help PNPRD to become a really effective school of work on the development of economically useful products and new drugs from plants and traditional remedies.

Now that as a result of the research and development programmes of PNPRD products are reaching the stage of commercialisation, greater attention would need to be given to export market and import substitution, and this should be reflected in the choice of the research and development programmes. Essential oils have a large demand in the international market. Their import in developed countries is not governed by strict regulatory laws as it is of drugs. During the second phase of this project, therefore, production of essential oils and aromatic chemicals from plants should form a part of the research and development programmes. Many important aromatic plants grow well in Thailand or can be easily cultivated. Mrs. Sasithorn Wasuwat, Project Director, has a good expertise in essential oils, perfumery chemicals and cosmetics. There would be need to include the cultivation of some plants as a part of the project, as source material for important drugs/essential oils, and to give added economic value to the planters if they can be used for inter-cropping or as underfoliage in large plantations such as those of rubber. The PNPRD has the resources of the Chantuk farm available to it; it has also good links with some premier Agricultural Research Institutions in Thailand. All this places PNPRD in advantage position to promote the cultivation of important plants and to undertake research and development work on their processing. In the choice of the research and development programme in the field of drugs and biologically active substances from plants, it should be more choosy and selective. It should develop expertise in a few selected areas, while maintaining its links with other institutions, nationally and internationally, whose collaboration it can seek to enlarge the spectrum of biological screens of the plants/products it takes up for study.

After discussion with Mrs. Sasithorn Wasuwat, it is suggested that the effort of PNPRD should be directed to the development of new drugs from

Thai Pharmacopoeia in the following fields :

- Anti-diarrheals,
- Anti-microbials, including anti-fungals,
- Cardiovascular drugs, including hypolipidemic agents,

Is suggested that PNPRD may also consider working on plants with potential as immunomodulators and adaptogens. In treatment of diseases in the traditional systems of medicine, main attention is given to the host; it is hypothesised that the healthy individual should not be susceptible to any disease. A number of drugs in the traditional systems, often named tonics, are directed to improve the human health in general and to increase the resistance to any disease or infection, and improve adaptation to any stressful situation; these have been termed "adaptogens" by some. It is not unlikely that some of them act as immunomodulators, and improve in a non-specific manner the immunity of the host to any infection, including against certain tumours. There is an interest in such agents as adjuvants for vaccines also. Discovery of new immunomodulators may thus be an important contribution that traditional pharmacopoeia can make to modern therapeutics. It may therefore be useful to investigate a few such drugs of the Thai Pharmacopoeia for their immunomodulatory and adaptogenic activity. This work should be started only if PNPRD can arrange for testing in some other institution in Bangkok.

Research and Development Programmes

In addition to work on projects carried over from Phase I, the following programme of work has been identified for Phase II of the project under different heads in consultation with Mrs. Sasithorn Wasuwat:

A. Production technology at pilot scale for products from :
   1. Aloe sp.
   2. Cananga odorata
   3. Curcuma longa (oleoresin and colouring matter)
   4. Ocimum basillicum/sanctum
   5. Stevia rebaudiana Bertoni for stevioside
   6. Vetiver
   7. Vinca rosea

In addition, exploratory work will be carried out on the cultivation and processing of the following plants, and if economic quantities of the plants become available, technology for the production of the active products would be developed:

1. Artemesia annua,
2. Cephaelis ipe acuanha,
3. Ipomea pes-caprae,
4. Mucuna pruriens,
5. Podophyllum emodi,
6. Rosa damascena,
7. Styrax benzoin, and
8. Valerian sp.

B. Standardisation of plant material for export

1. Ammomum sp.,
2. Curcuma longa,
3. Salix tetrasperma,
4. Smilax sp., and
5. Sterculia lychnofora

C. Development of new drugs from plant/traditional remedies

1. General screening

Now that a general screening capability for pharmacological and anti-microbial activity has been established, it is proposed to make a modest start in the general screening of plants growing in Thailand. The criteria of selection would be one or more of the following:

(a) Plants which are largely used in the remedies of the Thai pharmacopoeia,

(b) Plants which grow abundantly/specially in Thailand and have not so far been properly studied for the biological activity,

(c) Plants which have really important drug/biological active substances in recent years, but their correspondent species, though abundantly available in Thailand, have so far not been investigated.

34/Though

Though plants likely to possess immunomodulatory/ adaptogenic activity would be identified based on their reputation as toxicogenic in the Thailand Pharmacopoeia, but their biclogical evaluation will be carried out in collaboration with the Institute of Tropical Medicines, who have the facility for the testing and have agreed to do a biological evaluation.

Methods of the preparation of the biological activity fraction/constituent will be developed on plants which show biological activity. It is hoped that about ten plants per year will be collected and screened for the general pharmacological and anti-microbial activity,and those with no activity would be taken up for detailed biological evaluation.

2. Development of new spermicides

   Structure activity studies of terpinen-4-ol related compounds.

3. Testing of hypolipidemic and hypoglycemic activity of odourless garlic powder; pharmacological and clinical study. Testing of other plants/products of Thai Pharmacopoeia for their hypolipidemic and hypoglycemic activity.

4. The screening of the following plants for the activities mentioned against them will be carried out:
   - Acanthus ilicifolius as immunomodulator/adaptogen;
   - Alpinia galanga as anti-microbial;
   - Andrographis veninculata anti-microbial;
   - Nelumbo nucifera for CVS activities;
   - Phyllanthus indica as spermicidal;
   - Quisqualis indicum as spermicidal;
   - Salix tetrasperma as anti-fungal;
   - Sterculia sp. for immunomodulator/adaptogen; and
   - Uncaria sp. CVS activity

Some other plants mentioned in Thai Pharmacopoeia are largely used in traditional/household remedies in Thailand, particularly for the four conditions mentioned above will be investigated.

35/D.

D. Additional Strengthening

(1) Staff

Four scientists, three research assistants and four helpers would be required for the work that is expected to be carried out and for the new expertise needed to be developed during this phase of the project.

I had a discussion with Dr. Smith Kampermpool, Governor, TISTR, for these additional facilities, and he was in principle agreeable to provide them, subject to the availability of funds.

(2) Space

Additional space would be required for a suitably designed animal house facility needed for preclinical toxicology studies and for the pilot plant laboratory. A total space of about ten thousand square feet would be needed for these additional facilities.

	Total Period man/month	Cost US$
(3) Training		
- Chemical Technology)		
- Phytochemistry)	12	
- Preclinical Toxicology)		
(4) Study Tour	1	50,000.00
(5) Experts		
- Cardiovascular Pharmacology/ Hypolipidemic/Hypoglycemic/ Studies	12	100,000.00
(6) Equipment		
- Coulter Counter Complete set	(one)	50,000.00
- Drug Release Simulator		5,000.00
- Laboratory Milling Machine		5,000.00
- Lyophiliser to dry 2 lit/hr.	(one)	16,000.00
- Micronisor		4,200.00
- Microscopes	(two)	10,000.00
- Microtome	(one)	12,000.00

36/Automatic

(6) Equipment (cont'd)	Cost US$
- Automatic Tablet Machine Single Touch(Lab model)	6,000.00
- Microcomputer (128 K bytes,16 bit) with printer, disk drive, monitor and voltage stabilizer	5,000.00
- Microtome Knife Sharpener	4,000.00
- Molecular Distillation Still (one)	20,000.00
- HPLC Preparative Column (C_{18})	1,000.00
- PH Meter	3,000.00
- Process Cover	300.00
- Semi-automatic Analyser (for blood biochemical estimation)(one)	10,000.00
- Sieving Unit	4,500.00
- Tablet Disintegration Testing	3,000.00
- Tissue Embedding Console	11,000.00
- Tissue Processer	15,000.00
- Wide-bore Copillary Column for GC with Adaptor and Flow Accessory	800.00
	335,800.00
Miscellaneous/Spare Parts	14,200.00
Total	US$350,000.00

Annex 1

PNPRD Staff

	Names		Education	Year of Joining TISTR
1.	Mrs. Sasithorn	Wasuwat	M.Sc. (Pharmacy)	1966
2.	Dr. Sunthorn	Tandhanand	M.D., M.Sc. (Radio Biology)	1984
3.	Mrs. Prakongsiri	Boonkong	B.Sc. (Pharmacy) (Study Ph.D. in USA)	1969
4.	Mrs. Siripen	Jarikasem	M.Sc. (Pharmacology)	1978
5.	Mrs. Pattama	Soontornsaratoon	M.Sc. (Pharmacology)	1978
6.	Miss Acharaporn	Punruckvong	M.Sc. (Chemistry)	1979
7.	Dr. Montree	Koppinid	Ph.D. (Organic Chemistry)	1984
8.	Mr. Taweesak	Suntorntanasai	B.Sc. (Pharmacy) M.Sc. (Manufacturing Pharm.)	1984
9.	Miss Pattra	Lapikanon	M.Sc. (Organic Chemistry)	1982
10.	Miss Puttarin	Wannissorn	M.Sc. (Microbiology)	1984
11.	Miss Wilaiporn	Chamchaang	M.Sc. (Org.Chem)(Study Ph.D. in USA)	1982
12.	Miss Natthamas	Phootsree	M.Ed. (Biology)	1984
13.	Mr. Jakkarapong	Limpanussorn	M.Sc. (Pathology)	1983
14.	Miss Ubonwan	Pongprayoon	M.Sc. (Pharmacology(IFS Uppsala)	1982
15	Miss Chantara	Sankamoned	B.Sc. (General Science)	1984
16.	Miss Tuanta	Sematong	B.Sc. (General Science)	1982
17.	Miss Arubol	Chotipong	B.Sc. (Biology)	1984
18.	Miss Vannah	Kovitaya	B.Sc. (Pharmacy)	1985
19.	Miss Ananya	Supantavanich	B.Sc. (Microbiology)	1985
20.	Mrs. Kwanyeun	Wichapan	M.Sc. (Agriculture)	1966

TISTR (Cooperating Bodies)

1.	Mr. Chumnong	Hayakijkosol	Chemical Industry Department
2.	Mr. Visha	Tunvirachaisakul	Techno-Economics Division

Temporary Contractual Staff

1.	Dr. Somsak	Damronglerd	Chulalongkorn University
2.	Dr. Pramualmal	Suchaiit	Siriraj Hospital
3.	Mrs. Patcharee	Sunthonpalin	Siriraj Hospital
4.	Mr. Vichai	Reutrakul	Mahidol University
5.	Miss Noojaree	Prasitpan	Kasetsart University
6.	Mrs. Porntipa	Phicha	National Cancer Institute
7.	Dr. Krungkrai	Chenbhany	Siriraj Hospital
8.	Dr. Surapol	Patharakorn	Kasetsart University

Annex 2

Equipment Received During Last 3 Years (1983-1985)

A. From UNIDO

Already received

1. Centrifuge for Pilot Scale
2. High Performance Liquid Chromatograph
3. Rotary Evaporator (50 litre)
4. Accessories for Oscillograph
5. Preparative TLC Apparatus
6. Glass-lined Extractors (2) (ordered, expected anyday)

To be ordered

1. Vacuum Drum Drier

B. From TISTR

1. Refrigerate Superspeed Centrifuge for Semi-Pilot Scale
2. Analytical Balance
3. Vortex Mixer
4. Hot-Plate with Magnetic Stir
5. Heating Mantle 10 litr
6. Body Temperature Thermometer
7. Fume Hood

C. Others

Versatile Extractor

Annex 3

Products Developed by PNPRD

A. Products Transferred to Industry

- Garlic Natura, a water soluble garlic extract, in powder and capsules.
- Senna pods preparations, by GPO (and a private firm, according to the contracted project).
- Sliced ginger, improved quality, Thai Commodity Company, Ltd.

B. Products Developed and Ready to be Transferred to Industry

- Plygesal, an anti-inflammatory cream from Zingiber cassumunar.
- Pro-tincture of ginger, 8% solid contents.
- Anti-histaminic/Anti-venom cream from Ipomea pes-caprae.

C. Products Under Development

- Papain from papaya latex.
- Basil oil from ocimum basilicum.
- Anti-microbial cream from Alpinia galenga.
- Calcium sennosides.
- Ammomum xanthoides pro-tincture and oleoresin.
- Capsicum oleoresin.
- Vit. E concentrate and oryzanol from rice bran oil.

Annex 4

Publications: 1982 to 1985

1. Research Papers

   (1) MOKKASAMIT, M., NA-NAN, S., AIAMSOPA, P., CHALEOM CHAN, V., and KRITAPON, N., 1983. "Clinical Study of Garlic" Journal of Public Health Ministry, No. 2 vol. 7. July: 565-577 (In Thai)

   (2) SOONTHORNPALIN, P., WASUWAT, S., 1985 "Phakbung tha-le (Ipoemea Pes-caprae)" Siriraj Journal, No. 37, vol. 5, May: 329-333. (In Thai)

2. Handbooks

   Handbooks prepared under CO/NGO Cooperative Project "The Development of Cultivation and Quality Control Processing on Medicinal Plants for Export":

   (1) Handbook of curcuma longa, 1982

   (2) Handbook of Zingiber officinale, Cinger, 1982

   (3) Handbook of Capsecum sp., 1982

   (4) Handbook of Gamboge, 1985

3. Patent

   (1) Processing for the production technology of water soluble garlic extract in a spray drying powder form (1985).

4. TISTR Monographs

   (1) Abstracts on Medicinal Plants in Thailand, compiled by TNDC, series No. 6.

   (2) Selected Bibliography on Garlic, complied by TNDC, series No. 8.

   (3) A List of Thai Medicinal Plants.

5. Economic Feasibility Reports

   (1) Feasibility of papain production.

   (2) Feasibility of plygesal production.

6. Scientific Reports

   (1) WASUWAT, S. and NANDHSRI, P. "Gelatin capsule production from local raw material, pork skin". , 1982, 12 p. (In Thai)

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6. Scientific Reports (cont'd)

(2) WASUWAT, S., SOONTORNSARATOON, P., ROJANABHODI, W. PICHA, P. and NANDSRI, P. "A study on spermicidal efficiency of Thai indigenous medicinal plants. 1983, 26 p. (In Thai)

(3) HUET, R., WASUWAT, S., NANDSRI, P. and DISAYABOOT, P. "Study on Kradang-nga (Thai Ylang Ylang oil) 1982, 16 p.

(4) WASUWAT, S., SOONTORNSARATOON, P., PICHA, P., PONGPRAYOONG, O. LIMPANUSSORN, J. and SANDBERG, F. "Study on anti-neoplastic property, in vitro, of the detoxified extract of ratchadat, Brucea amarissima Desv. 1985

(5) WASUWAT, S., SOONTORNSARATOON, P., CHAMCHAANG, W., LIMPANUSSORN, J., PONGPRAYOON, U. "The study on the spermicidal effect of Nam Man Phlai, Zingiber cassumunar Roxb. 1985

(6) WASUWAT, S., SOONTORNPALIN, P. "The use of Ipomoea pes-caprae cream in the treatment of skin inflammation caused by the jelly-fish, 1985

7. Conferences Attended and Papers Presented

(1) Regional Workshop on Technology Transfer for Production and Processing of Medicinal and Aromatic Plants at Chiang Mai, 1983.

(1.1) Wasuwat, S., Bhanthumnavin, K., Boonyapra Pasara, N. "Country Report from Thailand for the Workshop on Technology Transfer for Production and Processing of Medicinal and Aromatic Plants".

(2) Fifth International Society of Horticultural Science Symposium on Medicinal, Aromatic and Spice Plants, Darjeeling, India (1985)

(2.1) Wasuwat, S., Soontornsaratoon, P., Chamchaang, W., Limpanussorn, J., Pongprayoon, U. "The Study on the Spermicidal Effect of Nam Man Phlai, Zingiber cassumunar Roxb.

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7. Conferences Attended and Papers Presented

(3) Wasuwat, S., Soontornpalin, P. "Investigation of Pharmacologically Active Principles of Ipomoea pes-caprae Linn., Roth. (Phakbung tha-le) in the "Tenth Conference of Science and Technology of Thailand," October 1984.

(4) Wasuwat, S., "Research and Development on Water Soluble, Natural Garlic Concentrated Powder (Garlic Natura) Seminar on Drug Development from Medicinal Plants, Bangkok, 1985.

(5) Proceedings of the National Conference on Agricultural and Biological Science, Twentieth Session (Plant Science) at Kasetsart University, Langkok, 1982.

(5.1) Wasuwat, S., Srichan, S. "Utilisation of senna leaves in the production of laxative drug".

(5.2) Wasuwat, S., Sunkumnord, D., "Gamboge".

(5.3) Wasuwat, S., Soontornsaratoon, P. "Oryzanol growth hormone in Thai rice bran".

Annex 5

Schedule of Visits and Meetings

Dates	
4 - 7 November:	TISTR. For discussion with Mrs. Sasithorn Wasuwat and staff of PNPRD.
8 November:	Nakorn Rachasima, TISTR Experimental Station Mrs. K[illegible]yeun Wichapan.
9 - 14 November:	TISTR. For discussion with staff of PNPRD.
12 November:	UNDP. Discussion with Mrs. N. Williams, Assistant Regional Representative.
15 - 16 November:	Chiang Rai, Natural Product Industry Company, Ltd. Mr. Anuwat Wongwan, Managing Director, Mr. Pipat Bampenwatana, Plant Manager.
" November:	Chiang Mai, Phuping Palace, Mr. Choowong Sucharitkul, Governor.
" November:	Siam Tobacco Export Company, Ltd. Mr. M. G. Fliakos, Assistant Manager.
17 - 20 November:	TISTR. Report writing.
19 November:	UNDP. Discussion of draft of report with Mr. N. Desai, Deputy Regional Representative and Mrs. N. Williams, Assistant Regional Representative.
21 - 22 November:	Songkhla, Haad Yai Rubber Experimental Station, Dr. Slearmlarp Wasuwat, Rubber Expert, Mr. Kasem Intharaskul, Director, Rubber Research Centre, Mr. Pichit Thasanakul, Rubber Expert.
" November:	Yala, Rubber Experimental Station Mr. Sunai Chindaraksa, Chief.
" November:	Narathiwat, The King's Project, Pikul Thong
23 - 26 November:	TISTR. Report writing.
27 - 28 November:	Rayong, Princess Maha Chakri Medicinal Plant Garden, Mab Kha Deputy Director Dr. Porn-Prom Hongsladaromya, PNPRD Horticulturist (part-time)
" November:	Marine Science Research Centre, Srinakarintharawiroj, Bangsaen Dr. Thavi Homchong, Rector, Dr. Pichai Sonchang, Marine Scientist,

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Annex 5 (cont'd)

Dates	
27 - 28 November:	Marine Science Research Centre, Srinakarintharawiroj, Bangsaen.
	Miss Wanta Thongna-ar, Marine Scientist,
	Miss Somporn Plearnchai, Marine Scientist,
	Miss Wanida Kamvej, Marine Scientist.
29 November:	Bangkok, Tropical Medicine Faculty, Mahidol University.
	Dr. Sawanat Dharawanich, Head, Immunology Division
	National Cancer Institute, Ministry of Public Health.
	Mrs. Porntipa Picha, Cancer Scientist,
	Dr. Nannee Rojanabhodi, Chief, Mutagen Division.
	Kasetsart University.
	Mrs. Sukanda Rojanasoonthorn, Head, Chemistry Department,
	Dr. Noojaree Prasitpan.
30 November:	TISTR. Finalisation of report.