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Research, Development and Production of Plant-based Medicaments in Africa. Case Study.

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TABLE OF CONTENTS

I.	Contemporary global context - Importance, at the biomedical level, of natural products in matters of health	1
II.	The Centre of Research on Pharmacopeoia and Traditional Medecine (CURPHAMETRA) in Rwanda	6
	A. Promotion of traditional Rwandaise medecine	8
	B. Use of officinal medicinal plants for the production	11
	C. Acclimatization of foreign medicinal plants	11
	D. Production of solvents and excipients	16
	E. Exploitation of economically viable plants	17
	F. Research and development of new medicines	18
III.	References	23

I. Contemporary global context - Importance, at the biomedical level, of natural products in matters of health

It is worth emphasizing the biomedical value of medicinal plants of which scientific medicine is often ignorant, especially as they play an important role, in the West as elsewhere, where pharmacy is concerned.

It will be noted that at present the medicines used in modern health treatment have a twofold origin :

- the synthetic or semi-synthetic substances created by man;
- the substances formed in the living cells of plants, micro-organisms or animals. These are referred to as "natural" pharmaceutical products.

Regarding the importance of these natural products in modern therapeutics, we need straightaway to stress the fact that about 50% of all medicines are such products : antibiotics, vitamins, hormones, digitaloids, alkaloids, etc. Investigations that have been going on for several years in industrialized countries show that one or several active principles occurring in the higher plants are found in 25% of prescribed medicines. In 1980, the total world market value of plant-based medicines was estimated at 8 billion dollars (1, 2, 3, 4)[1].

Moreover, if the primary application of natural products is pharmaceutical, the chemicals derived from plants have also many different applications, notably where food and cosmetics are concerned. Even if the world market is difficult to quantify, it is today considered to be valued at several billion dollars. A well-known example is that of essential and derived oils which are used as perfumes and food aromas, colouring in the food industry, semi-oxydizing agents, tanins, etc.

If we look at the role of natural products in an even wider context, we are reminded of the fact that the origin of several important groups of synthetic medicines is in nature : cocaine has served as a model for local anaesthetics, a series of parasympatholitics has been derived from atropine and a series of analgesics from morphine.

The synthesis of new medicines has been prompted by natural products for several reasons. The most important of these reasons is certainly the fact that man had had several centuries' experience with natural products of certain biological activity. With the birth of the synthesis of medicines, the first aim was to manufacture molecules having the same or a better activity than the natural product. Thus, for example, the synthesis of acetylsalicyclic acid (aspirine) was prompted by glycoside salicin which is found in the bark of the willow; quinine which is found in the bark of the cinchona served as model in the synthesis of a series of anti-malarial remedies. Subsequently, natural products have served as a starting point in the synthesis of important medicines. Two steroids isolated from plants, stigmasterol and diosgenine, are used to synthesize hormones like cortisone and hydrocortisone; enzymatic systems from certain micro-organisms bring about the necessary changes in the steroids to synthesize the hormones. Everywhere in the world, thousands of plants continue to have an application in medicine, such as they are or as pure biological substances.

Among the more than 260,000 different species of higher plants, i.e. seed plants, that grow on our planet, only 10% have been investigated chemically and/or biologically. This is why we must stress the fact that several new substances of certain biological activity will be discovered and make an important contribution, directly or indirectly, to so-called modern medicine.

Most plants grow in virgin forests which are mainly to be found in the South (in tropical and sub-tropical regions). These forests cover only 7% of the surface of our planet and yet harbour 2/3 of all species. As each year thousands of plants and animals disappear due to ever-increasing deforestation, innumerable compounds, developed over millions of years of complex co-evolution, have completely disappeared. This represents one of the greatest losses of DNA on the planet. This loss in DNA is all the greater as the genes of these plants have been developed in the highly competitive natural environment of the virgin forests.

Table I gives an idea of the medicines of plant origin currently used in modern therapeutics.

Table I : Medicines of plant origin

Drug	Plant
Atropine	*Atropa belladonna*
	Duboisia myoporoides
Ajmaline	*Rauwolfia vomitoria*
	Rauwolfia serpentina
Cocaine	*Erythroxylum coca*
L. Dopa	*Mucuna deeringiana*
Digitoxin	*Digitalis lanata*
Emetine	*Cephaelis ipecacuanha*
Ephedrine	*Ephedra spp.*
Forskolin	*Coleus forskohlii*
Hyoscyamine	*Datura spp.*
	Hyoscyamus muticus
Menthol	*Mentha spp.*
Morphine	*Papaver spp.*
Ouabain	*Strophanthus gratus*
Papain	*Carica papaya*
Physostigmine	*Physostigma venenosum*
Picrotoxin	*Anamirta cocculus*
Pilocarpine	*Pilocarpus jaborandi*
Quinine	*Cinchona spp.*
Quinidine	*Cinchona spp.*
Reserpine	*Rauwolfia serpentina*
Scopolamine	*Datura metel*
	Hyoscyamus niger
Theobromine	*Theobroma cacao*
Theophylline	*Theobroma cacao*
D-Tubocurarine	*Strychnos spp.*
	Chododendron spp.
Vincamine	*Vinca minor*
Vinblastine	*Catharanthus roseus*
Vincristine	*Catharanthus roseus*
Yohimbine	*Pausinystalia yohimbe*

The phytochemical agents mentioned in Table I are found in the internationally recognized pharmacopoeias or phytotherapeutic index[2].

[2] For an exhaustive list, one should consult the report of Farnsworth and his colleagues, which appeared in the WHO Bulletin in 1985 (5).

Note : The majority of these substances are always prepared from the plant, contrary to what is often thought. This does not mean that they have not been synthesized but that a commercially viable method does not exist. In other words, it is less costly to extract these active molecules from the natural raw material than to produce them by synthetic means.

But the medicines do not contain only pure molecules. Whole or purified extracts from plants are also used. Table II shows us some examples of plants used for the production of standardized whole extracts.

Table II : Medicinal plants used in the production of standardized whole or purified extracts

Plant	Standardized extract
Aloe spp.	Dry extract
Atropa belladonna	Dry extract
	Tincture
Capsicum annuum	Oleoresin
Centella asiatica	Purified extract
Cephaelis ipecacuanha	Soft extract
Cynara scolymus	Dry extract
Digitalis purpurea	Whole extract
Glycyrrhiza glabra	Whole or purified extract
Panax ginseng	Dry extract
Prunus africana	Purified extract
Rheum officinale	Dry extract
Valeriana officinalis	Dry extract
	Tincture
Zingiber officinalis	Dry extract
	Oleoresin

Despite such considerable medical and economic potential, 99% of the plants that grow in the virgin forests have not been studied up to the present time.

In the 1930s, the pharmaceutical societies went towards synthesis and molecular modeling to develop their medicines. But today the limits of chemical synthesis are as evident in the domain of what one can now imagine as a synthetic model as in the strictly scientific domain. It is a revealing fact that several pharmaceutical companies have again brought medicinal plants and natural products into their development programmes. This return to nature is well founded. It is estimated that there exist 1400 species of tropical that can be used to fight cancer. At the moment, two plants, *Psoralea corylofolia* and *Castospernum australe*, show promising signs in the struggle against AIDS.

Medical and economic interest in medicinal plants and the fact that they are localized for the most part in the countries of the South make obvious the need to launch new programmes of research and development in this part of the world in a process of North-South, and even South-South, co-development.

In developing countries, we know, it is almost impossible to pursue the strategy of the multinational pharmaceutical industries in the development of medicines both at the financial and the technological level. To develop a new modern medicine takes between 8 and 18 years and the cost is put at between 12 and 40 million ECUs. This cost cannot be borne by a poor country which, in addition, does not even have the means necessary to import all the medicines needed to cover basic medical care for its population and gets ever deeper into debt.

That is why, in respect of pharmacy, if the goal is to give autonomy to the different countries and regions of the globe and at the same time work towards planetary interdependence, sustainable lont-term development cannot be satisfied with the conditions and constraints pertaining to the production of the medicines on the basis of contemporary industrial strategies.

Most of the populations of the South first have recourse to traditional medicine and it is important to uphold traditional knowledge and know-how by combining it with science and modern techniques. There is a further advantage in that biodiversity and cultural diversity are thus safeguarded, even promoted.

The case of CURPHAMETRA, an innovator in this field, tells us something about the economic and socio-cultural potential where health is concerned which can be developed through networking and pilot projects for the other countries of the South and even to the benefit of the North. The initiative has already demonstrated its technical efficacy and social efficiency.

II. The Centre of Research on Pharmacopeoia and Traditional Medicine (CURPHAMETRA) in Rwanda

Rwanda is one of the smallest and poorest countries in Central Africa. It possesses a wealth of traditional medicine that is still very much alive.

This traditional medicine can be viewed as a rich resource and as having real potential in resolving the country's various health problems. But, sadly, in the countries where this form of medicine flourishes, it cannot find the socio-technical support needed to exploit it and get the most out of it. The World Health Organization has recognized the part that this medicine must play in its health programme for the year 2000 (6).

In Rwanda, as in other developing countries, around 80% of the population (7) has recourse to this medicine which is packed with a great mass of knowledge that is still secret and that needs to be saved quickly if it is not to disappear altogether. This is made all the more urgent by the fact that the arsenal of so-called modern medicines can no longer cope with the many different health problems and that these medicines are less and less available. It is very fortunate that peoples or groups of people who have no other recourse to medicine than the traditional variety have not abandoned it. It makes it possible to come upon new combined resources that guarantee endogenous development while opening up new capacities for further progress and codevelopment.

If, for peoples of the least developed countries like Rwanda, medicinal plants and traditional medicine retain such an important place, not only for their own benefit but also for that of the whole human race, are there not grounds for preserving this heritage or, better still, exploiting and developing it as a response to bad development in the South and in the North? Indeed is there not the obligation to do so? That at least was the idea that motivated certain researchers at the National University of Rwanda (N.U.R.) in their efforts to (re)direct their research activities and give them greater social usefulness with sustainable development as the goal.

It was with the aim of first preserving the health of the Rwandese people and rationally exploiting its natural resources that research work in this domain was undertaken at the end of 1971 at the Faculty of Medicine of the National University of Rwanda, in Butare, by a small network of young researchers. As a result of the growing interest shown by researchers in other faculties, an interfaculty and multidisciplinary research group was set up in 1977.

The development of this research work and the promising results obtained prompted the National University of Rwanda in 1980 to set up within its precincts the University Centre of Research into Pharmacopeoia and Traditional Medicine (CURPHAMETRA) as an autonomous and multidisciplinary research centre.

The principle goals assigned to CURPHAMETRA were at the start :

- to study and exploit traditional medicine;
- to undertake phytochemical and pharmacological research into Rwandese medicinal plants;

- to produce medicines from medicinal plants and other commercially viable products from local raw materials;
- to help in producing a Rwandese pharmacopoeia;
- to take part in providing university training in the domain of natural products.

Such objectives were difficult to get accepted in a university milieu given the prevailing mentality. A university centre of research simply does not go in for production. As there was no pharmaceutical industry in Rwanda, the researchers decided on their own initiative that, in order to give great practical value to the results of their research and to help with the development of a country lacking in medicines, they would create a pilot production department, even if that meant taking up arms against academia.

Apart from the involvement of the healer of which we will say more later, the centre has been able to extend its many intersectorial activities which include interdisciplinary research that goes beyond the strict bounds of chemistry and biomedicine, the development of new drugs, production and marketing.

At present, CURPHAMETRA forms part of the Institute of Scientific Research and Technology. This institute was created in 1989 by the Rwandese government with the aim of stimulating and favouring programmes of research necessary for the development of the country.

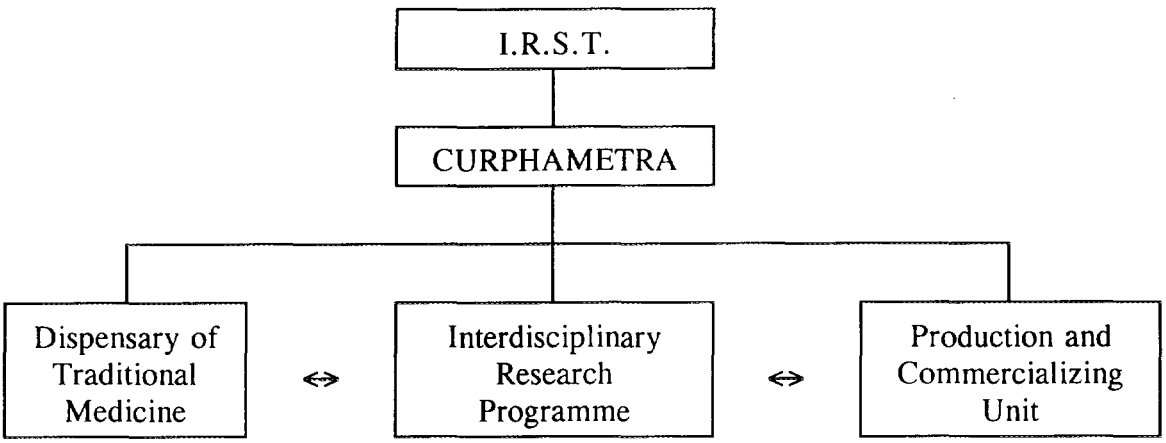
Nevertheless, the centre remains localized within the university campus so as to remain closely linked to education and research (training advanced students, associating academics from different disciplines with the work of the centre, etc.).

The production of medicines from local raw material, i.e. traditional prescriptions and medicinal plants, offers several significant advantages :

- it validates knowledge that has been handed down from previous generations;
- it reduces imports and so cuts the external debt;
- it creates jobs at several levels;
- it makes worthwhile medicines available to the population at a reasonable price;
- it opens up the possibility of exports;
- it protects and preserves the natural environment.

In order to achieve these objectives, CURPHAMETRA has as its disposal a dispensary of traditional medicine, an interdisciplinary research programme and a unit for the production of plant derived drugs (see Table III).

Table III : Chart illustrating CURPHAMETRA's structure and interaction



In order to attain as far as possible the objective considered of prime importance by the researchers (the development and production of drugs derived from local raw materials), a six-stage work plan was developed :

a) The promotion of traditional Rwandese medicine

b) The use of officinal medicinal plants for the production

c) The acclimatization of foreign medicinal plants

d) The production of solvents and excipients

e) The development of commercially viable plants

f) Research and development of new medicines.

A. Promotion of traditional Rwandese medicine

Health is man's most precious possession and any action that helps to preserve it deserves to be encouraged. The innate instinct of man to guard against illness and its consequences led him to empirical health care long before Hypocrates (8). Subsequently, modern medicine has been tried and tested. Several health systems have adopted it and employ it, but this does not mean that it has displaced traditional medicine. Around 80% of the populations in developing countries, especially in Africa, still rely on the healer.

The World Health Organization recognizes the importance of medicinal plants and adopted a resolution at the 31st World Assembly on Health, placing particular emphasis on their therapeutic value and the possible toxic effects. Furthermore, the same organization recommends that governments, scientific and medical communities of developing countries make themselves aware of the role played by traditional systems in the curative and preventive aspects of health. It also reminded its member states, at the 40th World Congress on

Health, of its position on research into traditional medicine, as well as the recommendations it made at the Alma-Alta Conference on basic health care.

Moreover, given the ever-increasing cost of modern medicine in an increasingly difficult economic situation, especially in developing countries, traditional medicine must be recognized and organized.

What is the situation in Rwanda? Traditional Rwandese medicine has for thousands of years been spread throughout the rural communities and the healer enjoys considerable estime. This state of affairs is linked particularly to the way the healer views a being, who is seen as both body and spirit. Bad health of whatever kind is interpreted as being the result of forces acting on both simultaneously (9). The Rwandese healer often acts as a phytotherapist, rites and incantations being reserved for certain psychiatric situations. His knowledge is as a rule inherited or an ancestral gift, which explains the esoteric character of certain practices. Remedies are prepared and distributed in different forms : decoction (boiling), infusion (soaking), maceration (pickling), extraction of juice or fumigation, and are often a mixture of several plants (10).

In the light of these practices which have sometimes demonstrated their therapeutic qualities, the healer should not be overlooked. The position of the Rwandese authorities on this subject is also unequivocal and its policy is to encourage and bring to light practices relating to traditional medicine. But how can this knowledge be spread to the whole population when it is known that charlatanism continues to increase?

It was by adopting a multi and interdisciplinary approach that CURPHAMETRA undertook to justify the use of this medicine and enrich it through scientific experimentation.

To help in the promotion of traditional Rwandese medicine we started *systematic ethnobotanical investigations*, we created a *Dispensary of Traditional Medicine*, and we began *checking on the efficacy of traditional remedies.*

- *Ethnobotanical Investigations*

The work of producing an ethnobotanical inventory had been begun a long time before by individual researchers.

To give two examples, we can mention :

- Lertrade, A. (1955) *La médecine indigène au Rwanda*
  Mémoires de l'Académie Royale des Sciences Coloniales, tome VIII, fasc. 1, Brussels.

- Durand, J.M. (1959) *Les Plantes Bienfaisantes du Rwanda et de l'Urundi*
  Groupe Scolaire, Butare (Rwanda).

A growing interest in these investigations led the researchers of CURPHAMETRA to systematize them in order to have an inexhaustible source of information. This was progressively conceived in respect of certain geographical areas (11, 12, 13). Other ethnobotanical investigations were carried out in the prefecture of Kibuyé (1978, all communes (14)), Butare

(1981, all communes), Gisenyi (1987, 10 communes), and Kibungo (1988, 6 communes).

This ethnobotanical inventory consists of information on medicinal flora collected from the healers themselves by a multidisciplinary team composed often of botanists, pharmacists, chemists and physicians.

In the course of these investigations, the healer explained what part of the plant was used, in what form he administered his medication and how he prepared it; likewise he gave the indications and contra-indications. Specimens were collected to make up the collections of the herbarium.

These investigations led to the scientific identification of several plant species known to our healers and which they employ in making up their prescriptions. This inventory serves as a tool for phytochemical and pharmacological research into plants appearing to have a particular value.

- *Dispensary of Traditional Medicine*

In order to benefit from the information in the possession of the holders of traditional know-how, CURPHAMETRA formed a Dispensary (or Community Clinic) of Traditional Medicine where healers and doctors could carry out consultations with patients. This dispensary began with six healers who formed part of the medical team. The role of the medical team was restricted solely to directing and following the progress of the patients and monitoring the therapy. It also gave advice on certain matters of general concern : cleanliness of the working surroundings and on the making up of the medicines, the size of the doses and the period of conservation.

Attempts to make diagnostic comparisons with what the healers think to be appropriate are in progress. This collaboration, which has been strengthened by the desire to have things organized, has allowed our healers to learn more about other health activities. The confidence of the consultant doctors has also increased. The healers themselves have agreed to reveal their secrets.

This working side by side will, in the near future, bring out the advantages of the interaction between traditional and modern medicine.

With the aim of consolidating the results already obtained in the field of traditional medicine, the task of forming and informing the healers in a variety of ways must be a priority of all those who undertake to promote and develop their knowledge. Helping the healers to find their place in the official structures must take precedence over their immediate integration into the officially recognized system of health.

In order to dispel certain discriminatory attitudes towards traditional medicine, it is essential to familiarize those who practise modern medicine with the principles of traditional medicine, with special emphasis being put on the therapeutic properties of the plants and traditional remedies, the worth of which has been proved. It is thus that the healers will also be able to adapt their diagnostic and therapeutic approach.

Research into traditional medicine must lead to an improvement in the way medicines are made up and their posology, while studying their toxicity. It will also have to contribute to the self-organization of the healers which will facilitate training in the area of diagnosis.

- *Efficacy of traditional remedies*

The results obtained (see below : Research and development of new medicines) by CURPHAMETRA from studying several medicinal plants constitutes additional proof of the value of the plants exploited by traditional Rwandese therapy. A new drug, an anti-mycotic, has even been developed as a result of information obtained from the healers. In the near future we should be able to propose a series of traditional remedies for integration into the system of basic health care.

The link, or better the network, of researchers and local healers, which grew out of personal contacts and developed in a climate of confidence, was the first necessity in the rational study of Rwandese medicinal plants. Without access to traditional data, it is difficult to obtain tangible results very quickly, even though it is possible to study plants selected at random and attain results. It has, however, been found that, by studying the prescriptions traditionally used, the number of medicinal plants found to be active is much higher (24). And what is more, it is the more complex approach allowed by the exchange and reciprocal training between doctors and local healers that is a determining factor in the rapid success of the work.

B. Use of officinal medicinal plants for the production

and

C. Acclimatization of foreign medicinal plants

We preferred to begin producing medicines from plants already known and described in pharmacopoeias for the simple reason that it took less time and did not require long and costly research (15, 16).

These plants are "Officinal Medicinal Plants" listed in the different pharmacopoeias - European, Belgian, French, English, etc. In this case, all one has to do is to follow the methods of dosage, analysis, extraction, etc., already described in these pharmacopoeias.

Moreover, if the medicines proposed are well known ones to be found in official pharmacopoeias, the doctor who has been trained in the modern system and who often knows nothing of the origin of the medicines he prescribes, has no reason to refuse these drugs. Subsequently, when the centre has been able to gain the doctor's confidence through its medicines which are thenceforth regarded as of good quality, it is easier to introduce new medicines derived from medicinal plants.

We made an inventory of the officinal medicinal plants that already grow in Rwanda and the following plants are grown or picked :

- *Datura stramonium* : the tincture is prepared from the leaves (anti-spasmodic),
- *Eucalyptus globulus* : the tincture and essential oil are produced from the leaves (pulmonary disinfectant),
- *Capsicum frutescens* : the liquid extract is prepared from the fruit (counter-irritant),
- *Plantago lanceolata* : the leaves are used for preparing the liquid extract (anti-tussive).

With a view to increasing the number of medicinal plants found in pharmacy, we introduced several well-known plants. At present, three plants are being grown and used for production purposes :

- tincture and liquid extract from the flower petals of *Calendula officinalis* (anti-inflammatory, healing substance),
- tincture and liquid extract from the green part of *Thymus vulgaris* (anti-tussive),
- essential oil from the leaves of *Mentha saccharinensis*.

For the production of these different extracts, an extraction and distillation unit was set up. For this type of production, we use driers, crushing machines, percolators, extractors, concentrators and distillers.

For the production of medicines, we have pharmaco-technical equipment at our disposal for making linctuses, solutions, tablets, ointments and powders. There is also a well-equiped laboratory for purposes of analysis and checking and we also have 100 hectares of land for growing medicinal plants.

For the moment, CURPHAMETRA produces several medicines using various plant extracts :

- a mouth disinfectant
- two cough syrop and a cough solution
- an anti-spasmodic syrop
- an anti-inflammatory healing ointment
- an anti-rheumatic solution
- four herbal teas

Mouth disinfectant

Oil of Eucalyptus	0.5
Menthol	0.5
Benzoic acid	3.0
Tincture of Eucalyptus s.q. ad.	100.0

Anti-cough syrop

Liquid extract of Plantago	10.0
Sodium benzoate	2.5
Ethyl alcohol	2.5
Syrop s.q. ad.	100.0

Anti-cough syrop

Oil of Eucalyptus	0.025
Potassium gaiacol sulfonate	2.5
Tincture of Stramonium	0.5
Sodium dibunate	0.2
Syrop s.q. ad.	100.0

Anti-cough solution

Tincture of Stramonium	15.0
Tincture of Thymus	20.0
Tincture of Eucalyptus	20.0
Sodium dibunate	2.0
Sodium benzoate	1.0
Distilled water	5.0
Ethyl alcohol s.q. ad.	100.0

Anti-spasmodic syrop

Tincture of Stramonium	5.0
Syrop s.q. ad.	100.0

Anti-inflammatory and healing ointment

Liquid extract of Calendula	5.0
Zinc oxyde	10.0
Lanoline	10.0
Vaseline s.q. ad.	100.0

Anti-rheumatic solution

Liquid extract of Capsicum	5.0
Methyl salicylate	3.0
Ethyl alcohol	50.0
Distilled water s.q. ad.	100.0

All these medicines are sold wholesale to the hospitals, health centres and community clinics or dispensaries and retail to the private pharmacies. A second series of medicines also derived from well-known plants will be developed and marketed in the near future.

Production method

This occurs in seven stages :

1. **Growing - picking**
   Each plant has its own growing requirements and an exact time at which it should be picked. We have 100 hectares of land that enable us to meet these requirements.

2. **Drying - crushing**
   The plants are dried in driers at 40°C and crushed mechanically. The distilling of essential oils is carried out using freshly picked plants.

3. **Analysis**
   The different batches of medicinal plants are analyzed so as to meet the norms set by the pharmacopeoias concerning :
   - the macro and microscopic aspect,
   - the dry weight,
   - the dosage of the active principle.

4. **Extraction**
   The percolation as well as the distillation are carried out at the production unit in accordance with the technological requirements for medicines.

5. **Analysis**
   A second analysis is required to conform with pharmacopeoic standards :
   - organoleptic examination,
   - dry weight,
   - alcohol content,
   - dosage of the active principle.

6. **Conversion to pharmaceutical form**
   The different extracts and raw materials manufactured in the production unit are given their pharmaceutical form : linctuses, solutions, ointments, etc.

7. **Inspection analysis**
   The inspection analysis is obligatory following stage 6. The results appear on the analysis certificate that accompanies the delivery of the medicines.

After these different stages, the medicine is packed (for wholesale or retail delivery) and marketed. Even if the quality of the drug is the primary objective, it is absolutely essential, despite the low income of local consumers, that the packaging be suitable and attractive for sale in private pharmacies so that it can compete with imported medicines. Also explanatory leaflets for the different medicines have been produced for the benefit of doctors, pharmacists and paramedical staff. What is more, one of the pharmacists from CURPHAMETRA makes regular visits to the private pharmacies, doctors and hospitals in order to follow the progress of the medicines and do some advertizing to promote the drugs.

It should be noted that several new medicines have been developed and manufactured (see below : *Research and development of new medicines*).

Tables IV and V show the evolution of our small-scale production. This evolution in production and marketing has enabled us to programme and start production on a large scale.

We have begun to promote intensively our products and we foresee that from 1992-1993 we shall be able to start large-scale production so as to satisfy the Rwandan market.

Table IV : Evolution of the annual production[3]

Products	Quantity		
	86/87	87/88	88/89
- ethyl alcohol 95°	1362 L	3540 L	9260 L
- anti-spasmodic linctus *(D. stramonium)*	360 kg	1490 kg	2350 kg
- anti-cough linctus *(P. lanceolata)*	45 kg	560 kg	1985 kg
- anti-cough linctus *(E. globulus, T. vulgaris, D. stramonium)*	76 kg	640 kg	1420 kg
- anti-cough solution *(E. globulus, T. vulgaris, D. stramonium)*	11 kg	7,5 kg	37 kg
- mouth disinfectant solution *(E. globulus, M. saccharinensis)*	11 kg	7 kg	47 kg
- anti-rhumatic solution *(C. frutescens)*	12 kg	100 kg	254 kg
- anti-scabies[4] solution *(N. mitis)*	-	-	450 kg*
- anti-inflammatory ointment *(C. officinalis)*	-	50 kg	107 kg
- anti-scabies disinfectant ointment *(N. mitis)*	-	-	208 kg*

* for a period of seven months

[3] From the point of view of these products meeting national needs, the quantity is still insignificant given that we started production on a pilot scale.

[4] This was the first new drug that we produced from a traditionally used Rwandese medicinal plant, the Neorautanenia mitis.

Table V : Annual evolution of the production of the various pharmaceutical forms

Products	Quantity		
	86/87	87/88	88/89
- Linctuses	481 kg	2690 kg	5763 kg
- Solutions	34 kg	114,5 kg	788 kg
- Ointments	-	50 kg	315 kg
- Alcohol	1362 L	3540 L	9260 kg

As can be seen, there are three pharmaceutical forms being produced : linctuses, solutions and ointments. Other pharmaceutical forms will be developed and manufactured, namely tablets, powders, suppositories and capsules.

Self-financing for the production unit will be reached around 1994. What is more, by not just increasing production capacity but also by broadening the range of medicines and developing new drugs, we aim to become financially independent both in respect to prduction and in development research by around 1997.

D. Production of solvents and excipients

The development and the production of medicines do not only involve the use of active principles but also require solvents and excipients which account for a large part of the production cost.

1. *Solvents*

- In the production of various extracts from medicinal plants (e.g. tinctures, liquid and soft extracts) a mixture of **water** and **ethanol** is used. These two solvents are prepared in the production unit.

- A simple distiller serves to produce distilled water.

- Ethyl alcohol is obtained from the molasses at the sugar refinery (17, 18). After the diluted molasses has fermented, it is distilled a first time (ethyl alcohol 60-80°), then the alcohol is passed through a carbon active reactor to remove the impurities and finally the alcohol is rectified to 95°.
  For the moment, the production capacity is 12,000 L of 95° ethyl alcohol; this capacity will be extended to reach a minimal capacity of 45,000 L a year.
  This alcohol does not serve only as a solvent for extraction purposes but is also commercialized as a disinfectant.

- For the needs of the laboratory we distil, on a small scale, raw petroleum to obtain **petroleum ether**.

2. *Excipients*

Excipients often play a large part in the production of medicines. The few possibilities that can be explored in the near future are :

- starch, which can be produced from cassava; it serves among other things in the manufacture of tablets;
- beeswax, which is produced to some extent everywhere in the country, can be used in the preparation of certain ointments.

It is absolutely essential to start research projects for developing solvents and excipients using local raw material to reduce importation costs in the manufacture of medicines.

For example, it is possible to produce several other drugs from molasses by changing the fermentation parameters (micro-organism, temperature, etc.) (19).

E. Exploitation of economically viable plants

Here it is a question of plants which provide essential oils, tanins, dyes, alkaloids, etc., and that have a certain economic value.

- Several plants have been analyzed for their **tanin** content with a view to finding exploitable plants. These tanins could replace the plant tanins imported by the local tanneries (20).

- For the food industry and the textile industry, plants must be found containing **dyes**. In Rwanda several sorts of *Indigofera* exist, plants that produce indigo, a well-known dye for fabrics. A new biological dye, which colours the material yellow, has been developed from the fungus *Pisolithus arhizus* (21).

- **Alkaloids** : a method for extracting industrially berberine from the roots of *Thalictrum rynchocarpum* has been developed (22). Berberine is an anti-amoebic drug much used in Asia.

- **Essential oils** : one of CURPHAMETRA's research programmes is concerned with the exploitation of essential oils locally and with their exportation. The essences have a variety of applications : in pharmacy, hygiene, food, cosmetics, etc. Rwanda imports more than one and a half million ECU's worth of essential oils and related products a year (23) which shows the economic value attached to the exploitation of essential oils.

At present, CURPHAMETRA produces the oils *Eucalyptus globulus* and *smithii* and *Mentha saccharinensis*, used in the preparation of several medicines. In the production of an anti-mosquito cream and candle, the following plants are used : *Pelargonium graveolens, Eucalyptus citriodora* and *Cymbopogon citratus*.

The substantial production of essences for the Rwandese cosmetics industry is also envisaged.

F. Research and development of new medicines

- At CURPHAMETRA, the studies carried out on medicinal plants are for the most part based on the information provided by the local healers in the course of the *ethnobotanical investigations*.

- These plants are the subject of a *botanical study* in order to determine the exact scientific name of the plant.

- Subsequently, the extracts of these plants, prepared with the help of various solvents, are submitted to a series of *biological and pharmacological tests* to discover one or other useful biological activity.
  At present, CURPHAMETRA is able to carry out several biological and pharmacological activities :

  - anti-bacterial (24, 25)
  - anti-fungal (26)
  - anti-pyretic (27)
  - hepato-protective (28, 29)
  - anti-spasmodic (30)
  - anti-mitotic (31, 32)
  - insecticide-pesticide (33, 34)
  - acaracidal (35)
  - anti-protozoan (36, 37)
  - cardiotonic (38)
  - anti-convulsive (39)
  - anti-diarrhoeal (40)
  - anti-scabies (41)

- After a study of the literature, *phyto-chemical bio-guided studies* are carried out on those plants that display useful biological and pharmacological activity in order to obtain the active principles possessing the previously identified activity.

- Recourse is had to various techniques of spectrometry to determine the chemical structure of the active principles that are isolated from the plants.
  As CURPHAMETRA does not yet possess a large part of the necessary equipment, it maintains good relations with foreign laboratories and collaborates with them. Likewise, certain biological tests, for which the Centre does not possess the equipment and appropriate biological models, are also carried out in collaboration with foreign laboratories.

- After the chemical and pharmacologico-toxicological studies of the medicinal plants, *clinical trials* are begun. If the results are positive, the necessary steps can then be taken to obtain *legal recognition* of the new medicines.

In what follows, we describe the development of three new drugs :

- an anti-scabies solution and ointment from the tubers of *Neorautanenia mitis*

- a pesticide from the leaves of *Tetradenia riparia*

- an anti-mycotic ointment from the roots of *Pentas longiflora*

We are here concerned with the first new drugs developed in Rwanda by CURPHAMETRA, something that was done from Rwandese medicinal plants.

a) A drug to treat scabies

The Rwandese peasant has long employed the powder of the tubers of *Neorautanenia mitis*, mixed with butter, to treat his calves for scabies (49).

In a biological screening of several medicinal plants we found that the tuber of *N. Mitis* possessed acaricidal and anti-scabies activity (41).

The bio-guided phyto-chemical study led to the isolation of several isoflavones of which the 12a-hydroxyrotenone was responsible for the biological activity being sought (42, 43, 44, 45).

Here it should be noted that in the past, in medicine, rotenone was used to treat scabies.

An anti-scabies solution and an anti-scabies disinfecting ointment were prepared from an alcohol extract (total extract) from the tuber of *N. mitis*.

After preliminary trials on rabbits infected with scabies, a clinical study on man was carried out. More than 500 patients suffering from scabies or infected with scabies were treated with the solution or the ointment. A comparative study of these drugs with a known anti-scabies drug and a two-fold blind study formed part of these clinical studies (46). All the persons treated were cured. We found no side effects, either with the solution or with the ointment.

At present, the solution and the anti-scabies ointment are being marketed in Rwanda by CURPHAMETRA.

It should be pointed out that scabies is a very common parasitosis, in the town as well as in the country. It is often accompanied by a secondary infection (47).

Anti-scabies solution

Tincture of Neorautanenia

Anti-scabies and disinfectant ointment

Liquid extract of Neorautanenia	5.0
Vioform	1.0
Lanoline	10.0
Vaseline s.q. ad.	100.0

b) A pesticide

For Rwanda, the development of pesticides from local drugs, i.e. medicinal plants, is acquiring capital importance, given the quantity of pesticides being imported to support the priority programme for self-sufficiency in food and, in contrast, the poor purchasing power of the population. In 1985, the importation of pesticides exceeded 1,400 tonnes and cost 2.2 million ECU's. Moreover, these pesticides are reserved almost solely for development projects (48).

The first new pesticide was developed from the leaf of *Tetradenia riparia.*

This plant is very well-known to traditional Rwandese medicine. It is grown around houses for medical reasons, but it is also used for preserving beans in traditional silos (11, 50).

Biological screening showed that the leaves of *Tetradenia riparia* possessed several useful biological and pharmacological activities (24, 26, 32, 37). The bio-guided phytochemical study led to several new molecules (51, 52, 53, 54) of which the 8(14),15-sandaracopimaradiene-7a,18-diol is the most active principle. This new diterpenediol displayed several activities : an anti-microbial activity (55), an anti-spasmodic activity (30), an anti-trichomonas activity and inhibited the growth of wheat rootlets (32).

The anti-microbial activity has been used against *Pseudomonas Solanacearum*, an important potato pest in Rwanda.

A formulation with an alcohol extract from the leaf of *T. riparia* has been perfected.

"In vitro" and "in vivo" trials have been carried out formulation. After trials in the greenhouse and in the fields ("in vivo"), we found that our product completely prevented the development of the bacteria and resulted in an increase in the potato yield of roughly 35% compared with the sets that were not inoculated and not treated and of roughly 120% with those sets that were inoculated and not treated (57).

The formulated extract, which can be used in a spray or in a simple solution, is ready to be marketed.

Pesticide solution (concentrated)

Dry extract of Tetradenia	200 g
Tensiofix B	50 g
Ethanol 80°	950 ml
(Dilution in water 200 x)	

c) An anti-mycotic

One of the local healers from our Dispensary of Traditional Medicine used the powder from the root of *Pentas longiflora* to treat pityriasis versicolor, a dermatological disease of fungal origin.

In a study involving several plants used as anti-fungals in traditional medicines, a high level of activity was found in the roots of *P. longiflora* (26). This led to the isolation of the active principle, a naphthoquinone.

An ointment manufactured from the total extract of the roots of this plant was tested clinically on 80 persons suffering from pityriasis versicolor. In this case too, all the persons treated with our new anti-mycotic ointment were healed, without any undesirable effects being observed (58).

At present, it only remains to receive the official go-ahead to begin production and start marketing the product.

Antimycotic ointment

Dry extract of Pentas	5.0
Lanoline	10.0
Vaseline s.q. ad.	100.0

It goes without saying that for this research to be brought to a satisfactory conclusion there was a great deal of scientific collaboration both within the country and with the outside world.

Several academics from the Faculty of Medicine, Science and Agronomy at the National University of Rwanda and researchers from other institutions like the I.S.A.R. (*Institut des Sciences Agronomiques du Rwanda*) carry out research projects within an in collaboration with CURPHAMETRA. The latter also takes students from several faculties who do their degree thesis on one or several Rwandese medicinal plants.

There exists, moreover, intense collaboration with the Faculty of Economic and Social Sciences and Management to help the Centre develop the commercial section of the production unit.

Scientific collaboration between the Laboratory of Organic Chemistry at the Faculty of Agronomy (University of Ghent - Belgium) and CURPHAMETRA exists in order to determine the structure of the molecules (active principles) which have been isolated in Rwanda from medicinal plants. Several biological trials currently being conducted at CURPHAMETRA, such as the search for anti-protozoan agents, have been developed at the Institute of Tropical Medicine in Antwerp (Belgium) where several Rwandese researchers took a six-month training course.

All this collaboration, inside and outside the country, has led to joint publications.

It has to be noted that the Pilot Plant for the production was financed by the Rwandese Government, the Belgian Administration for Development Cooperation, the United Nations Industrial Development Organisation and the World Health Organisation.

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ANNEX 1 :

Financing of the production-unit of CURPHAMETRA

From 1971 to 1979, research work on medicinal plants in order to develop phytomedicines was sponsored by the National University of Rwanda by means of small research grants. In 1980, at the creation of CURPHAMETRA, the University voted an annual working budget for the research center.

The development of this research work and the promising results obtained for the production of plant-derived medicaments incited the United Nations for Industrial Development - UNIDO - in 1980 to start a project at CURPHAMETRA for the development and production of phytomedicines : Project no DP/RWA/80/003/A/01/37.

This UNIDO project was the first important step for the exploitation of the aromatic and medicinal plants in Rwanda. The project was the basis for the creation of a Rwandese pharmaceutical industry.

The UNIDO project included :

- the installation of a pilot plant for the processing of aromatic and medicinal plants (distillator, concentration, multipurpose extractor, percolators, steam generator);

- equipment for the laboratory of analysis and control of all products;

- training at site by international experts (cultivation of plants, production and analysis);

- study tour for the national director;

- training abroad at appropriate institutions (production and analysis, cultivation).

With this pilot plant, CURPHAMETRA started the production of essential oils, different kinds of plant extracts (tinctures, liquid extracts, decoctions and concentrated extracts) several phytomedicines (solutions, syrups, ointments) proposed by the UNIDO expert, were developed.

The total cost of the UNIDO project was $ 450.000,-. The land for cultivation, the building plot, the housing, a working budget and the necessary human resources were donated by the Rwandese Government.

Due to the success obtained by the UNIDO project, the Belgian Government started in 1983 the second phase of the project, necessary for the commercialization of the phytomedicines and other products at a larger scale. A complementary and supplementary equipment for the production unit and the laboratory of analysis and control was obtained. The project also provided the necessary equipment for the processing of the different extracts into finished products (i.e. pharmaco-technical

equipment for the production of tablets, ointments, syrups, capsules, ...) and for the production of ethyl alcohol 96° at a larger scale.

The total cost of the Belgian project (investment and working budget) was $1.600.000,-.

Some additional equipment for production and analysis was obtained through WHO for a value of $ 100.000,-.

ANNEX 2

A. Development of phytomedicines started from well-known medicinal plants.

To start production of phytomedicines, the selected plants should be "Officinal Medicinal Plants", i.e. plants already studied and described in different Pharmacopoeias. The development of such plant-derived medicines do not require long and costly research and there is no reason for the medical doctor to refuse the prescription of these medicaments.

The following procedure can be considered :

a. The "Officinal Medicinal Plants" growing in the country should be inventoried.

b. The selected plants should be available in large quantity or large-scale cultivation should be possible.

c. Foreign well-known medicinal plants could be introduced in order to increase the number of "Officinal Medicinal Plants".

d. The technologies used for the production of the plant extracts should be simple and the production cost low.

e. The solvents (water and alcohol) used in the processing of the plants should be produced locally or otherwise available at a low price.

CURPHAMETRA programmed different phases in his production process starting with the most simple technology.

First phase :

- Production of necessary solvents (water and alcohol) by fermentation, distillation, purification and rectification.

- Production of medicinal teas starting from the dried and ground medicinal plants.

- Production of essential oils by steam distillation.

- Production of tinctures and liquid extracts by simple percolation.

These extracts are used in the formulation of solutions, syrups and ointments.

Second phase :

- Production of concentrated extracts (total fluid or soft extract) by rotavapor or thin-layer evaporator.

- Production of dry extracts by spray dryer of cabinet air-dryer.

These extracts are used in the formulation of ointments and tablets.

Third phase :

- Production of purified extracts and pure compounds.

The necessary equipment for the production of these extracts was not yet available at CURPHAMETRA.

B. Development of new phytomedicines

At CURPHAMETRA, we started the development of new plant-derived medicaments for external use only. For the development of new phytomedicines for internal use we did not have, at that moment, the necessary infrastructure and competence for detailed pharmacodynamic, pharmacokinetic and toxicological investigations.

For the production of a novel plant-based medicament we used the following necessary steps :

1. Selection of suitable plant material from the traditional medicine.

2. Botanical investigation.

3. Biological-pharmacological screening.

4. Bio-assay guided isolation of active principle(s).

5. Structure determination.

6. Detailed biological-pharmacological evaluation.

7. Formulation.

8. Clinical trials on animals.

9. Clinical trials on men.

10.Development of analytical methods.

11.Registration by the National Drug Authorities.

12.Cultivation of plant.

13.Production of plant extract.

14.Production of phytomedicine formulation.

15.Commercalization.

In accordance with this plan, we developed the following new phytomedicines :

- an antimycotic ointment;
- an antidandruff shampoo;
- an antiscabies solution;
- an antiscabies and disinfectant ointment;
- an antiparasitic shampoo.

ANNEX 3 :

Methods of analysis and quality control

The quality control and the standardization, necessary for safe and efficacious phytomedicines, starts with a well-defined plant material through a defined extraction procedure and ends with a quantitative method for one or more active ingredients.

For the "Officinal Medicinal Plants" which are listed in different Pharmacopoeias, the methods of analysis, dosage, extraction, ... to be followed are already described.

Analysis executed at CURPHAMETRA :

a. For the dried crude plant material :

- Macroscopic and microscopic aspect
- Dry weight
- Determination of ash, sulfated ash and acid-insoluble ash
- Dosage of active principle(s)
- Microbiological assay

It has to be noted, that the necessary plant material is produced at CURPHAMETRA.

b. For the different plant extracts :

- Organoleptic examination
- Dry weight
- Alcohol content
- Dosage of active principle(s)

c. For the finished products :

- Alcohol content
- Dosage of active principle(s)

N.B. : for all stage of production there is an analysis certificate.

The quantity of the active principle(s) (dosage) is determined by using classic chemical methods, spectrometric analysis and different chromatographic analysis such as TLC, HPLC and GC. If the identification of an active principle is not possible, a chromatographic fingerprint is made to identify a characteristic substance or mixture to ensure the quality of the product.

In the case of production of new phytomedicines, which are not yet described and for which no pharmacopoeia monographs exists, a new monograph was supplied and set out in the same way as in Officinal Pharmacopoeias. For the new phytomedicines of CURPHAMETRA (the antiscabies and antimycotic), it was also possible to develop a method for analysis by means of chromatographic technics as the active principles were characterized.

ANNEX 4 :

Product information

- To the health personnel :

  - Explanatory brochures for the different phytomedicines have been realized for the medical doctors, pharmacists and paramedical staff.

  - For the new phytomedicine brochures have been produced with the following documentation :

    - use in traditional medicine
    - biological-pharmacological activities
    - phytochemical study
    - experimental pharmacology
    - formulation of the medicine
    - clinical trials
    - indications
    - method of application
    - tolerance
    - formula and presentation
    - complete literature

  - A pharmacist of CURPHAMETRA makes regular visits to the medical doctors, private pharmacies and hospitals in order to explain and to promote the phytomedicines and to follow the efficacy of the products.

  - The medical doctors receive regular free samples.

- To the consumer :

Besides, the necessary suitable and attractive packaging of the phytomedicines, the labeling of the products and the packaging insert should be understandable to the consumer/patient.

The following information is necessary :

- name of the product
- quantitative list of active ingredients
- therapeutic properties
- indications
- contraindications, warnings and precautions
- adverse effects
- administration and dosage
- duration of use
- presentation
- conservation
- expire date

- lot number
- address of producer

As not all information, ideally required, may be available, the National Drug Regulatory authorities should determine their minimal requirements.