International Organization for Chemical Sciences in Development

Working Group on Plant Chemistry

CHEMISTRY, BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES OF AFRICAN MEDICINAL PLANTS

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African traditional healer and *Harpagophytum procumbens* (Pedaliaceae)

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13. Research, development and production of plant-based medicines in Africa. Example of Rwanda.

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Introduction

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 program for the year 2000.

In Rwanda, as in other developing countries, around 80% of the population 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 co-development.

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.

The Center of Research on Pharmacopoeia and Traditional Medicine in Rwanda: CURPHAMETRA

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 Center of Research into Pharmacopoeia and Traditional Medicine (Curphametra) as an autonomous and multidisciplinary research center. 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 center 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 center 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 favoring programs of research necessary for the development of the country.

Nevertheless, the center 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 center, 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 program and a unit for the production of plant derived drugs (see Fig. 13.1.).

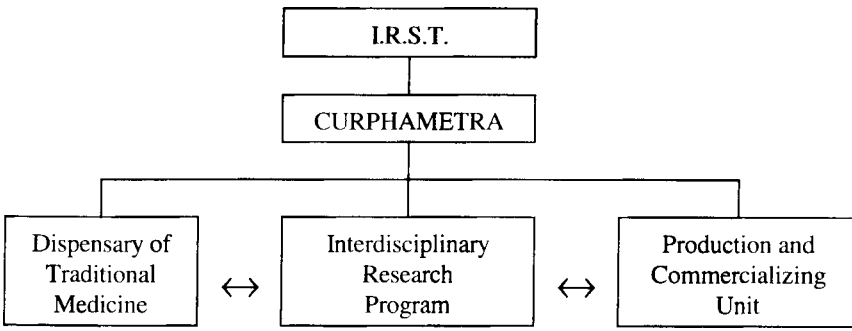

Fig. 13.1. Chart illustrating Curphametra's structure and interaction.

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 :

1) The promotion of traditional Rwandese medicine.
2) The use of officinal medicinal plants for the production.
3) The acclimatization of foreign medicinal plants
4) The production of solvents and excipients.
5) The development of commercially viable plants.
6) Research and development of new medicines.

Promotion of traditional Rwandese medicine

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 - 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 (Van Puyvelde *et al.* 1975, 1977a and 1982). Other ethnobotanical investigations were carried out in the prefecture of Kibuyé (1978, all communes), 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.

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 antimycotic, 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 (Boily and Van Puyvelde 1986). 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.

Use of officinal medicinal plants for the production and 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.

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 center has been able to gain the doctor's confidence through its medicines which are therefore 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 (antispasmodic),
- *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 (antitussive).

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* (antitussive),
- 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 dryers, 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-equipped laboratory for purposes of analysis and checking and we also have 100 hectares of land for growing medicinal plants.

Curphametra produces several medicines using various plant extracts :

- a mouth disinfectant
- two cough syrup and a cough solution
- an antispasmodic syrup
- an anti-inflammatory healing ointment
- an antirheumatic solution
- four herbal teas

All these medicines are sold wholesale to the hospitals, health centers 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.

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 advertising 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*).

Table 13.1. shows the evolution of our small-scale production. This evolution in production and marketing has enabled us to program 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 13.1. Annual evolution of the production of the various pharmaceutical forms

Products	Quantities		
	86/87	87/88	88/89
- Syrups	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 L

As can be seen, there are three pharmaceutical forms being produced : syrups, 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 production and in development research by around 1997.

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.

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 (Mungarulire *et al.* 1980). 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 distill, on a small scale, raw petroleum to obtain petroleum ether.

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.

Exploitation of economically viable plants

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

- Several plants have been analyzed for their tannin content with a view to finding exploitable plants. These tannins could replace the plant tannins imported by the local tanneries (Dubé *et al.* 1979).
- For the food industry and the textile industry, plants containing dyes must be found. In Rwanda several sorts of *Indigofera* exist, plants that produce indigo, a well-known dye for fabrics. A new biological dye, which colors the material yellow, has been developed from the fungus *Pisolithus arhizus* (Van Puyvelde *et al.* 1983).
- Alkaloids: a method for extracting industrially berberine from the roots of *Thalictrum rynchocarpum* has been developed (Dubé and Van Puyvelde 1979). Berberine is an anti-amoebic drug much used in Asia.
- Essential oils : one of Curphametra's research programs is concerned with the exploitation of essential oils for local use and for exportation. The essences have a variety of applications : in pharmacy, hygiene, food, cosmetics, etc.

At present, Curphametra produces the oils of *Eucalyptus globulus*, *E. smithii* and *Mentha saccharinensis*, used in the preparation of several medicines. In the production of an antimosquito cream and candle, the following plants are used : *Pelargonium graveolens*, *Eucalyptus citriodora* and *Cymbopogon citratus*. The substantial production of essential oils for the Rwandese cosmetics industry is also envisaged.

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 : antimicrobial (Boily and Van Puyvelde 1986; Van Puyvelde *et al.* 1983), antipyretic (Hakizamungu 1981), hepato-protective (Van

Puyvelde *et al.* 1989), antispasmodic (Van Puyvelde *et al.* 1987a), antimitotic (Van Puyvelde *et al.* 1988), insecticide-pesticide (Weaver *et al.* 1992), acaracidal (Van Puyvelde *et al.* 1985), antiprotozoan (Hakizamungu *et al.* 1992), cardiotonic (Uwilingiyimana *et al.* 1990), anticonvulsive (Mukarugambwa *et al.* 1990), antidiarrhoeal (Maikere-Fanyo *et al.* 1989), antiscabies (Heyndrickx *et al.* 1992)

After a study of the literature, *phytochemical 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.

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

Three new products were developed :

- an antiscabies solution and ointment from the tubers of *Neorautanenia mitis*
- a pesticide from the leaves of *Tetradenia riparia*
- an antimycotic ointment from the roots of *Pentas longiflora*

A drug to treat scabies - The Rwandese farmer employs the powder of the tubers of *Neorautanenia mitis* (Leguminosae), mixed with butter, to treat his calves for scabies.

In a biological screening of several medicinal plants we found that the tuber of *N. Mitis* possessed acaricidal and antiscabies activity (Heyndrickx *et al.* 1992). The bio-guided phytochemical study led to the isolation of several isoflavones of which 12a-hydroxyrotenone was responsible for the biological activity (Van Puyvelde *et al.* 1987b). Here it should be noted that in the past, in western medicine, rotenone was used to treat scabies. An antiscabies solution and an antiscabies and 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 humans was carried out. More than 500 patients suffering from scabies were treated with the solution or the ointment. A comparative study of these drugs with a known antiscabies drug and a double blind study formed part of these clinical studies (Van Puyvelde *et al.* 1990). All the persons treated were cured (Figs. 13.2. and 13.3.). We found no side effects, either with the solution or with the ointment.

The solution and the antiscabies ointment were commercialized by Curphametra.

Antiscabies solution:	Tincture of Neorautanenia	
Antiscabies and disinfectant ointment:	Liquid extract of Neorautanenia	5.0 g
	Vioform	1.0 g
	Lanoline	10.0 g
	Vaseline *s.q. ad.*	100.0 g

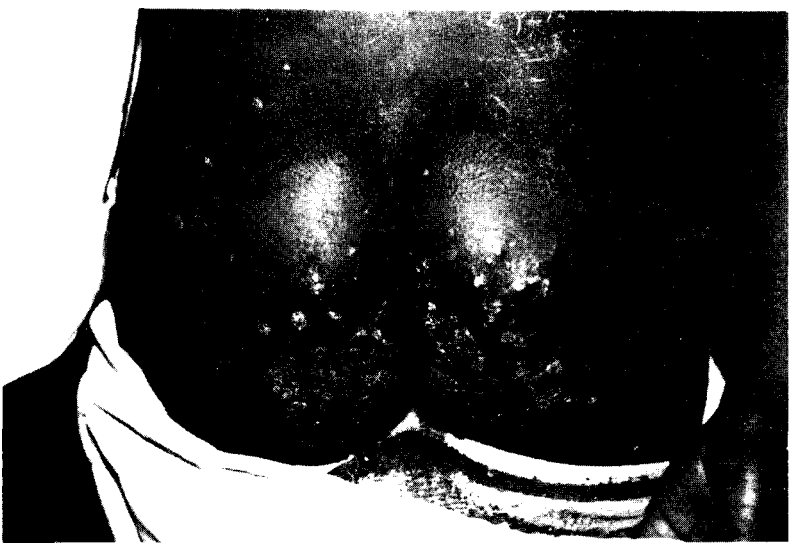

Fig. 13.2. Patient with infected scabies before treatment

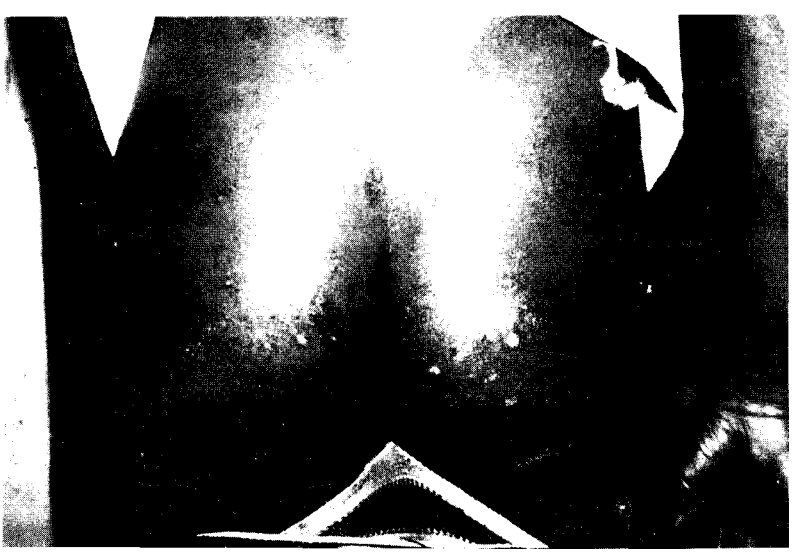

Fig. 13.3. Same patient, 1 week after treatment with *Neorautanenia mitis* preparation .

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 program for self-sufficiency in food and, in contrast, the poor purchasing power of the population. In 1985, the importation of pesticides exceeded 1,400 tones. Moreover, these pesticides are reserved almost only for development projects.

The first new pesticide was developed from the leaf of *Tetradenia riparia* (Lamiaceae). This plant is well-known in traditional medicine. It is grown around houses for medical reasons, but it is also used for preserving beans in traditional silos (Van Puyvelde *et al.* 1975). Biological screening showed that the leaves of *Tetradenia riparia* possessed several useful biological and pharmacological activities (Boily and Van Puyvelde 1986; Van Puyvelde *et al.* 1988; Hakizamungu *et al.* 1992). The bio-guided phytochemical study led to several new molecules (Van Puyvelde *et al.* 1979 1981 and 1987c; De Kimpe *et al.* 1982) of which the 8(14),15-sandaracopimaradiene-7a,18-diol is the most active principle. This new diterpenediol displayed several activities : an antimicrobial activity (Van Puyvelde *et al.* 1986), an antispasmodic activity (Van Puyvelde *et al.* 1987), an antitrichomonas activity (Hakizamungu *et al.* 1988) and inhibited the growth of wheat rootlets (Van Puyvelde *et al.* 1988). The antimicrobial activity (Hakizamungu *et al.* 1988) 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 with the 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 (Butare 1987).

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)	

An antimycotic - One of the local healers from our Dispensary of Traditional Medicine used the powder from the root of *Pentas longiflora* (Rubiaceae) to treat pityriasis versicolor, a dermatological disease of fungal origin. In a study involving several plants used as antifungals in traditional medicines, a high level of activity was found in the roots of *P. longiflora*. 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 antimycotic

ointment were healed, without any undesirable effects being observed (Van Puyvelde *et al.* 1994).

Antimycotic ointment	Dry extract of Pentas	5.0 g
	Lanoline	10.0 g
	Vaseline *s.q. ad.*	100.0 g

Final observations

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 Center develop the commercial section of the production unit.

Scientific collaboration between the Laboratory of Organic Chemistry at the Faculty of Agronomy (University of Gent - 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 antiprotozoan agents, have been developed at the Institute of Tropical Medicine in Antwerp (Belgium) where several Rwandese researchers took a six-month training course. The Institute of Pharmacognosy and Phytochemistry, of the University of Lausanne participated in developing Curphametra.

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 Organization and the World Health Organization.

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