

Eugenia Jambolana: Madagascar

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Summary

For more than 30 years, the Malagasy Institute of Applied Research (IMRA) has been researching the traditional medicines and food plants of Madagascar that, despite being nutritionally and medically valuable, often are overlooked and underused by local people. This case study is about one of IMRA's most interesting and successful projects.

Eugenia jambolana Lamark is a species of big tree that grows on the central high plateau and east coast of Madagascar. It is a member of the Myrtaceae family to which myrtles belong.

Eugenia jambolana produces small purple plums, called java plums (or rotra in Malagasy), that have a very sweet flavor, turning slightly astringent on the edges of the pulp as the fruit becomes mature. Java plums are rich in sugar, mineral salts, vitamins C and PP (which fortifies the beneficial effects of vitamin C), anthocyanins, flavonoids and other useful ingredients.

Although Malagasy folk healers have successfully used *Eugenia jambolana* to relieve the symptoms of diabetes, its full potential has never been exploited. In addition, the fruit could be made into jams, jellies and health drinks, but a general lack of knowledge and interest exists in collecting, using and preserving java plums. Until IMRA launched its valorization of *Eugenia jambolana* project in 1970, much of this valuable resource had been ignored and left to go to waste.

The project's main aims were, first, to identify ways of using the plant and its fruit and, then, to introduce these techniques and products to the public. Although ways of preserving the fruit to produce a range of tasty and healthy foods were one of the project's outputs, most of the work went towards developing the potential of *Eugenia jambolana* seeds in the treatment of diabetes and building on the experience and informal findings of centuries of local usage.

The result was a commercially produced drug called Madeglucyl®, which has since been widely used by Malagasy diabetes patients. Along the way, scientists worked to find the best ways of collecting the original plant material, which meant training hundreds of rural families to identify the best seeds to pick. Ways of preserving the seeds were another aspect of scientific study. Researchers also concentrated on making this product acceptable and attractive to the country's population. In this effort they were aided by its appeal as a safe, natural drug with no toxic side-effects. Finally, issues of industrial production and commercialization within Madeglucyl® had to be addressed.

Background and Justification

Modern scientific exploration of traditional African medicine and healing has three main benefits:

- It is an important source of scientific and medical development.
- It helps protect useful local cultural practices and introduce these practices on the world stage.
- It provides an easily accessible and affordable source of effective drugs for the population of Africa and beyond.

In this case, IMRA's work also helped to protect the environment and slow deforestation. In the past, *Eugenia jambolana* trees often were cut down for housing construction, furniture-making or fuel. Since the species' medical uses have been discovered and publicized, such destructive practices have declined. At the same time, rural people have generated extra income from seed collection and the entire country has enjoyed the trees' fruits which have been processed into jams, jellies and drinks.

Madeglucyl®

IMRA's promotion of traditional medicine in the treatment of diabetes dates back to 1965 when two of the institute's professors, Albert Rakoto-Ratsimamanga and Suzanne Ratsimamanga-Urverg, began to work

with local healers to find out what they were doing. The professors' curiosity was aroused when they came across a very simple way of diagnosing diabetes: healers were asking their patients to urinate close to an anthill and then observing how the ants reacted. Ants usually avoid urine, but the urine of people suffering from diabetes contains a great deal of sugar that attracts the insects. The ants' behavior therefore implied that a patient was diabetic. Once the professors observed how healers then prescribed a plant — *Eugenia jambolana* — it was time to start serious laboratory work on the potential medicinal properties of this plant.

From 1967 until 1985, the professors studied and experimented with *Eugenia jambolana* seeds at both IMRA and the National Center of Scientific Research (CNRS) of the Faculty of Medicine at the University of Paris. The formulation that they came up with and called — Madeglucyl® — contains 1 percent active ingredient. Tests established that the drug is stable and that it is consistently effective as a treatment for diabetes.

Trials on laboratory animals were carried out over several generations of rats (particularly the sand rat) that were found to be the most appropriate laboratory animal for this stage of research. The trials showed that Madeglucyl® did indeed alleviate the symptoms of diabetes. Additional experiments and tests showed that it is not toxic, does not cause cancer or lead to the malformation of embryos and has no other detrimental side-effects. Finally, clinical trials are being held on thousands of diabetes patients in Madagascar and, recently, in Germany and the United States.

On 18 December 1997, Madeglucyl® was registered as a licensed medicine in Madagascar.

The following are some of its main features:

- When used on patients with type 2 diabetes, it returns glycemia rates to normal levels within three to six months in 75 percent of cases. It has proven particularly effective for obese patients, whose glycemia rates start to decline after 15 days and return to normal within three months (again in 75 percent of cases).
- It reduces, by nearly 40 percent, the daily insulin required by type 1 insulin-dependent patients.
- In some cases, it has improved the functioning of the kidneys and relieved some of the eye complications that diabetes can cause.
- It acts by improving the ability of the body's tissues to absorb glucose thus enhancing the effectiveness of insulin.

Rural Income

In Madeglucyl® production, the seeds (which are the most important part of the tree) must be collected and processed when they are at their peak. It took IMRA several years to devise an efficient seed collecting system. The problem proved complicated because the plant products that the institute needs perish very quickly. The obvious people to go to were those who live in rural areas where the trees grow and, in its early days, the *Eugenia jambolana* seed collecting network was based on one that had been established to collect other plants, including *Centella asiatica*.

After brief training, rural people took to seed collecting and drying enthusiastically (the work is relatively easy and the pay is good for people who have few alternative sources of cash income). By 1998, total annual harvests of 20 tones were being gathered during relatively short collection seasons.

IMRA carries out the selection and grounding of seeds so that all parasites and insects can be killed. Powdered seeds are stored in bags, holding 10 or 50 kilograms (kg), made from a special polyethylene that allows moisture to get out but not in. In this way, the powder can be stored until it is needed.

Food Source

Although the production of jams and jellies may seem a humble research objective compared to a cure for diabetes, java plums are a recognized source of valuable nutrition.

Eugenia jambolana trees require a humid climate and the fruits mature during the rainy season. The plant does not grow well in such arid, dry areas such as southern Madagascar. The fruit's season runs from February to April and, depending on its age and growth stage, each tree can produce 15 to 180 kg of fruit, representing 5 to 60 kg of seeds. Madeglucyl® uses only the seeds. Therefore, researchers looked for

ways to exploit the fruit both commercially and on a household scale for rural families who were collecting the seeds.

The challenges were to:

- Discourage rural people from cutting down the valuable trees, which they did to supply fuel and construction materials or to clear land for cultivation.
- Teach them to squeeze the seeds from the fruit under running water and then dry the seeds in the open air.
- Make the most of the leftover fruit by incorporating it into their own diets as a valuable source of nutrition.

These challenges were answered, first, by demonstrating how the trees could serve as a valuable source of income and, second, by developing recipes for using the fruit to make homemade jam.

IMRA is now searching for partners in the food industry so that java plum jams and jellies can be produced and marketed on a commercial scale. Food researchers also are looking for other ways of using this fruit and have had particularly exciting results from a well-received wine. The plums, both fresh and dried, also may have potential in the expanding exotic fruits market of developed countries.

Patents and Commercialization

Madeglucyl® was registered as a New Drug Application (NDA) with the government of Madagascar in the Ministry of Health in December 1997. An initial license was registered in Paris in 1984. A second license, issued in 1996, grants the product international recognition.

IMRA, which has been marketing medical products for more than 25 years, now sells some 40 medicines in addition to medicinal cosmetics and food additives, throughout Madagascar. At present, some 6,000 Malagasy diabetic patients receive Madeglucyl®, most free of charge as part of the ongoing clinical trial process.

Partnerships

The compounds that make Madeglucyl® effective against diabetes were extracted, isolated and developed in partnership with the French-based Rhône Poulenc Rorer pharmaceutical company.

Other partners and collaborators in the project include: the World Health Organization (WHO); private companies — SOAMADINA Limited Company (Madagascar), CFAO-EURAPHARMA (France), Afrique — Initiatives (Belgium), and Carlesimo Foundation (France); the public health sector in Madagascar — Ministry of Health, National Drug Agency, Faculty of Medicine, Faculty of Science, and Polytechnic School; the Medical Practitioner Association (Madagascar); universities and international institutes — Catholic University of Louvain (Belgium), Faculties of Pharmacy at Rheims, Chateney and Lille (France), Natural History Museum (France); Institute of Health (Italy).

Replicability

IMRA is a private foundation, recognized by the government of Madagascar and the World Health Organization (WHO) as a collaborative center. It is committed to drug regulation, quality control of imported and local drugs, and legislation to protect and authorize the use of new drugs. It guarantees free access to and exchange of information and products with national and international partners.

The findings of the *Eugenia jambolana* project could easily be applied to other countries, especially those bordering the Indian Ocean, where the plant grows naturally and extensively. The process for producing Madeglucyl® from the seeds of the plant is protected by an international license, but commercial agreements could be made with the public and private sectors of other developing and developed countries to allow this safe and affordable diabetes treatment to be made available to patients worldwide. IMRA is particularly interested in working with national health authorities in African countries to establish commercial links for the sharing of Madeglucyl®.

Lessons Learned

The main challenge focussed on how to use traditional knowledge that had never been scientifically tested to produce a useful modern drug. Many key people involved in the project had graduated from universities in Europe with strong commitments to use their training to advance their own country's development. Their professional experience acquired in the industrialized world combined with their personal dedication to their developing home country helped see them through the 15 years of research and analyses that led to the development of Madeglucyl®.

The second challenge — making the *Eugenia jambolana* drug (and food products) acceptable to the public — was more easily and quickly overcome. It helped that the team was working with a locally known product that already had a place in the country's traditional culture. The reasonable cost of the drug and the ready availability of the fruit were added incentives.

Impact

In recent decades, many medicinal plants from the South have been developed and exploited by pharmaceutical companies from the North without the benefits being shared with the native country. Take, for example, *Catharantus roseus* that grows in Madagascar but is harvested and used by a Northern industry as an important anti-cancer agent. Madagascar has derived no profits from this effort.

IMRA's *Eugenia jambolana* project has helped to redress this imbalance and, for once, the economic and health benefits of a new development are being enjoyed, principally, by the native country.

Among the positive impacts of the project are its contribution to local health and nutrition. Today many people enjoy an extra source of employment as a result of collecting the seeds and cultivating the trees.

New uses of *Eugenia jambolana* also are potentially sustainable, as long as appropriate laws, regulations, standard operating procedures and good manufacturing practices are put in place and supported by the ministries of health, drug regulatory agencies and environment and nature protection institutions at the national and international levels.

Future Plans

IMRA currently is establishing partnerships with French and other European private companies to build a production unit where drugs can be manufactured according to international manufacturing standards and practices. The unit will initially produce enough Madeglucyl® to meet the demand in Madagascar. Over the next two to three years, the market will be expanded to other parts of Africa.

As a quality control center, IMRA is helping to put in place a post-marketing surveillance network for new drug applications. It is also establishing a diabetes network where patients can obtain information and support for various therapy options and be given follow-up care. Finally, IMRA is a consultant to the ministry of health, offering advice on how to establish and implement new drug registration procedures.

Institutional Profile

IMRA was established in 1957 by Albert Rakoto Ratsimamanga as a training and research center. Its headquarters is located near Antananarivo, the capital of Madagascar. In 1993, it was given official government recognition as a nongovernmental organization. Since then, as a WHO collaborative center, it has contributed to national economic development by training researchers and students, training and assisting the rural population, and protecting biodiversity. The institute's directors are Albert and Suzanne Ratsimamanga. It has a permanent staff of about 150 and offers temporary and seasonal employment for about 15,000, mostly rural, people.

IMRA's short-term objectives are to promote medicinal plant drugs and indigenous foods as an effective way of promoting national sustainable economic development.

It has four main divisions:

- Department for research into ethnobotany, phytochemistry, pharmacology and toxicology.
- Department for the production and quality control of drugs, essential oils and food medicines.
- Health center offering free health care and medical analysis.

- Botanical garden for collecting and protecting endangered medicinal plant species.

Among the 40 plant-based drugs that IMRA has developed and formulated for the treatment of a wide range of diseases in Madagascar are:

- TMM, an anti-leprosy treatment.
- Madecassol, a wound-healing agent based on extracts of *Centella asiatica*.
- Madeglucyl®, an antidiabetic drug that this study has examined.
- Chloroquine-resistant *Plasmodium falciparum* used in the fight against malaria.
- *Hernandia voyronii* and *Strychnos myrtoïdes* from which new alkaloids are extracted.

All of these drugs are inexpensive and can be afforded by much of the Malagasy population.

Implementing Institution

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