

Blood *of the* DRAGON

The Sustainable
Harvest and
Replanting of the
Croton lechleri Tree

By Kelly Saxton Lindner



Croton lechleri tree.
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Many people indigenous to the Peruvian Amazon lack options when it comes to employment. Some have to travel 6 hours by powerboat to sell fish to the nearest town, which can occasionally result in the fish spoiling before they arrive at their destination. Some Peruvians have few agricultural crops that they can farm to financially support their families other than coca (*Erythroxylum coca*, Erythroxylaceae)—the leaves of which are traditionally chewed in the highlands as a way to increase energy and prevent altitude sickness and sometimes used to produce cocaine. Because of such limited work opportunities, some Peruvians find it difficult to pay the registration fees required to enroll their children into school and purchase even the most minimal of school supplies, such as pencils and books. Some are also unable to build hospitals, high schools, soccer stadiums, and other things that could improve their communities.

However, several communities in Peru are now able to obtain necessities by working with Napo Pharmaceuticals Inc. of San Francisco, California.* These communities help to sustainably harvest the latex of a tree in the Peruvian rainforest, which Napo then turns into a drug that has been shown to be effective in treating various forms of diarrhea (including cholera- and HIV-related diarrhea). This drug may be able to successfully treat these diseases on a global level in the near future.

What is the Blood of the Dragon?

Sangre de drago or “dragon’s blood”—also referred to as *sangre de grado*—is the red latex found in a number of tree species from the genus *Croton* (Euphorbiaceae), common in the lower montane and rainforest basin regions of several Andean countries (Colombia, Ecuador, Peru, and Bolivia), as well as northern Argentina and southeastern Brazil.¹ Although many species of trees from the family Euphorbiaceae produce a milky white sap, *Croton lechleri* and other species found in Mexico, Central America, and tropical and subtropical South America are all characterized by their viscous red latex.

The latex of *C. lechleri*—which is dark red when taken from mature trees but lighter in color, sometimes orange, within younger trees²—has been used by healers for centuries to treat diarrhea and various ailments, including gastrointestinal problems, respiratory infections, skin infections, mouth disturbances, wounds, and herpes simplex.^{1,2,3,4} The traditional dose of latex is 5–10 drops applied topically over lesions or mixed in water, juice, milk, or alcohol and ingested 1 to 3 times a day for up to 3 weeks.³ There are no known adverse events related to the internal use of the latex,

*Napo’s name derives from a major tributary of the Amazon, which flows out of the province of Napo in Ecuador and joins the Amazon downstream from Iquitos, the former rubber-tapping center in Peru.

Left photo: A *Croton lechleri* tree used by Napo for reforestation in the buffer zone near Parque Nacional Cordillera Azul in Northern Peru. Several thousand small seedlings cover the forest floor. The area is prepared to maximize production of seedlings as part of natural forest regeneration and reforestation process. Photo ©2009 Steven R. King

and because of the tree's wide distribution and the historically recognized effectiveness of its sap, it's one of the most common traditional medicines in Latin America.

Napo has been researching and working with *C. lechleri* for many years, and its intellectual property (obtained from the now-defunct Shaman Pharmaceuticals, which had employed an ethnobotanical approach to drug discovery) goes back over 20 years. Napo has endeavored to find the best growing conditions for *C. lechleri*, the most effective ways of sustainably harvesting and replanting the tree, the most productive methods for collecting the latex, and the best ways to efficiently employ local indigenous people, who are in need of adequate income. (Most earn a relatively minuscule amount of money compared to wages in developed countries). Over the last 2 decades, more than 30 studies on the biology, ecology, distribution, economics, and reforestation have been conducted by scientists in different Andean countries regarding *Croton* trees. Napo selected *C. lechleri* because of its biological activity and because it is a well known and widespread pioneer tree species.³ Studies have found that in rainforest areas of the Andean Amazon region (at a general altitude of 300–700 meters), there's an average density of 3 to 10 of these trees per hectare. The general altitude range of the tree is 300–2,000 meters.

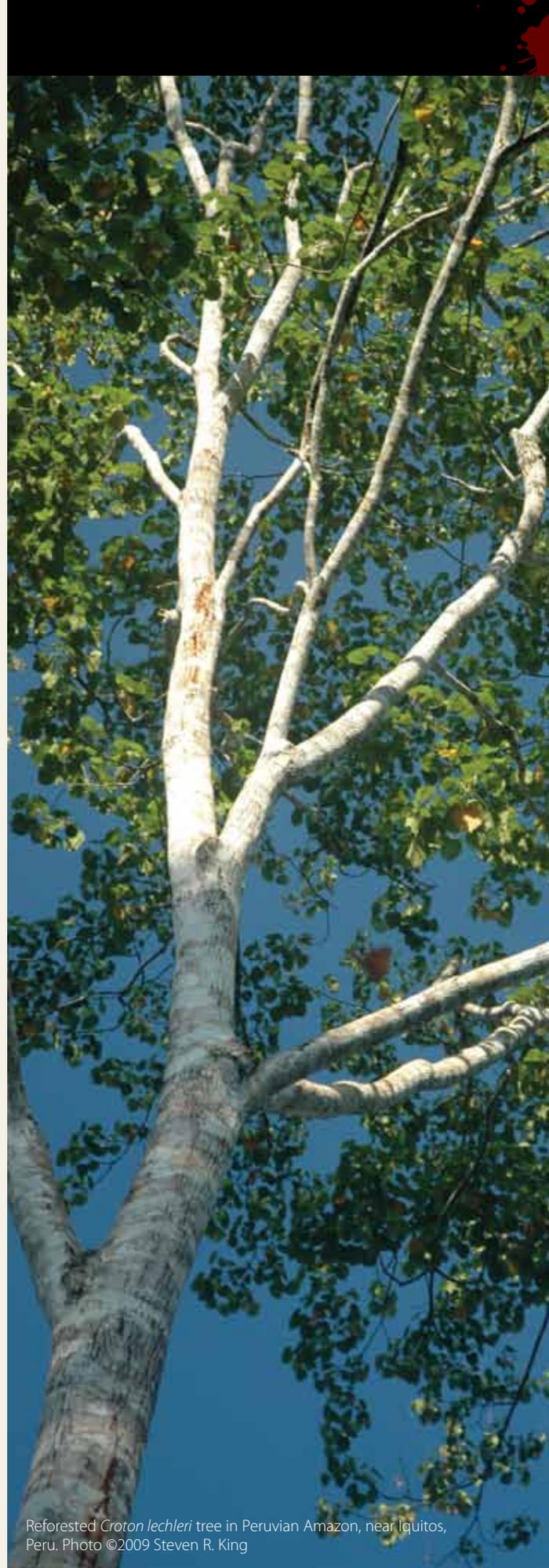
Napo has used the tree's latex to create a drug able to combat HIV/AIDS-related diarrhea, severe cholera-induced fluid loss, traveler's diarrhea, and diarrhea-predominant irritable bowel syndrome (IBS). This drug, made with a highly purified proanthocyanidin oligomer called crofelemer, which Napo has isolated from the *C. lechleri*'s latex, has shown overall effectiveness in approximately 1,700 randomized patients in double-blind, placebo-controlled, clinical trials, with no apparent adverse effects, even in patients as young as 3 months of age.^{2,3} There have been many pre-clinical and clinical trials conducted on crofelemer, and Napo has received fast-track status from the US Food and Drug Administration (FDA) for its development of crofelemer for its IBS and HIV indications.^{5,6,7,8,9}

Napo has entered into an agreement with Direct Relief International (DRI), a medical assistance and disaster relief agency based in Santa Barbara, California, to provide the drug at cost to children afflicted with cholera and diarrheal diseases of developing countries once its safety and efficacy has been fully established in children.¹⁰ Napo also plans to collaborate with the International Centre for Diarrhoeal Disease Research (ICDDR) in Bangladesh for the same purpose; Napo has already collaborated with ICDDR on studies treating adult cholera patients with crofelemer.

Cholera is an infection that causes severe diarrhea, which leads to dehydration and can cause death, sometimes within the first 6–18 hours of infection.¹¹ Every year approximately 2.5 million children under the age of 5 die due to dehydration caused by various forms of diarrhea, such as cholera. This occurs primarily in developing countries, and it stems from such causes as limited access to clean water. Since crofelemer has an anti-secretory mechanism of action that blocks chloride ions and subsequent water secretion, this keeps the gut from losing too much excess fluid and can prevent dehydration-related death caused by cholera or HIV-related diarrhea.^{2,11,12} In fact, it improves bowel function in many conditions that involve prominent secretory diarrhea. Crofelemer's effectiveness on diarrhea-predominant IBS is still being evaluated, but it has been shown to reduce pain in this condition, which is one of the primary complaints of those who suffer from IBS.¹³ Crofelemer also acts locally on the gastrointestinal tract, instead of being absorbed into the body, which gives it a higher level of efficacy than other treatments and limits the potential for adverse effects.^{2,12} Most anti-diarrheal agents paralyze or slow processes in the gut, causing constipation, and cannot be taken for more than 24 hours.

Tapping versus Felling

Researchers at Napo originally hoped that *C. lechleri* trees could be harvested much like the rubber tree (*Hevea brasiliensis*, Euphorbiaceae), through the use of a machete or tapping tools to tap or cut the bark and drain



Reforested *Croton lechleri* tree in Peruvian Amazon, near Iquitos, Peru. Photo ©2009 Steven R. King

There are no known adverse events related to the internal use of the latex, and because of the tree's wide distribution and the historically recognized effectiveness of its sap, it's one of the most common traditional medicines in Latin America.



Reforestation of wild collected *Croton lechleri* sapling in secondary forest near Huallaga River in Peruvian Amazon.
Photo ©2009 Steven R. King

desired latex while leaving the tree standing and healthy.³ The *Hevea* species can be tapped repeatedly for latex without damage to the tree. *Croton lechleri*, however, demonstrated a high mortality rate when this tapping method was implemented and did not yield much latex.¹⁴

To understand why their efforts toward tapping *C. lechleri* were not successful, employees of what is now Napo sent bark samples to the Royal Botanic Gardens in Kew, England, where Paula Rudall, PhD, head of the micromorphology section at Kew, examined the differences between *Croton* and *Hevea* bark. Dr. Rudall found that the laticifers, which produce the latex in the *Hevea* trees, are articulated and regenerate when cut. Species such as chicle (*Manikara zapota*, Sapotaceae), which is used to make chewing gum, and jelutong (*Dyera costulata*, Apocynaceae), which has a lightweight wood used in many things like pencils, are also articulated, meaning that they can be tapped repeatedly without destruction to the trees.³ The laticifers in *Croton* species are non-articulated and do not regenerate when cut. Dr. Rudall concluded that this morphological difference is what causes the *Croton* trees to “go dry” faster when tapped and causes the high mortality rates in the trees.

Therefore, it was decided that it was actually more sustainable to cut down the whole tree and drain all available latex at once, which creates a much higher yield of latex than tapping, and then replant a new tree in its place. The fact that *C. lechleri* has been documented to be a fast growing pioneer tree species also greatly influenced this decision.

The Harvesting of *Sangre de drago*

Local people with experience harvesting *C. lechleri* latex taught the company that the best yield of latex is obtained early in the morning (although observations show that harvesting during the full moon actually tends to yield the most latex). Workers typically harvest during the hours of 4:30 am and 9:30 am, since too much heat from the sun can cause the tree to lose water and yield less latex. Rainwater can also dilute the latex, so dry weather conditions are recommended. Through years of research, collectors have determined that it is best to harvest trees that have reached their 6th or 7th year or older and are about 27 cm (10–11 inches) in diameter at a minimum, as this increases the yield of latex.⁴ If harvested in this manner, these trees can consistently yield an average of 3 to 4 liters of latex per tree.

To perform the harvesting, first a slash is cut into the tree's bark to make sure that the tree has latex, as sometimes a tree is too young or damaged to produce. The tree is left standing if there is very little or no latex. If the tree has sufficient latex, it is then felled onto 2 pre-cut perpendicularly laid logs and propped so that the base of the tree is higher than the top. Full shallow circles are cut into the bark 1 cm wide, every 15 cm, with a special knife called a *rasqueta*, which looks similar to a hooked or bent machete. Plastic containers are placed under each cut to catch the latex as it drains.

Napo continues to refine its knowledge of the best ways to harvest. In fact, Mario Pariona, a conservationist who works with one of Napo's 3 harvesting

Latex of *Sangre de drago*. Photo ©2009 Michael Powers





“The *Croton* tree has managed to be a source not only of medicine but also a source of jobs for indigenous people and farmers in the rainforest of the Amazonia in Peru”

and replanting subsidiaries in Peru, says that each day he and others go into the Andean or Amazonian towns to find out more about the best harvesting conditions from locals. For instance, they attempt to discern “how to select the trees with the best contents of latex, how to define the suitable diameter of the trees for the harvest, the best seasons for the extractions, and moon phases and hours of the day for the best results,” said Pariona (written communication, July 15, 2009).

Cesar Gregorio Lozano Diaz, who oversees 4 primary harvesting and reforestation sites for Napo, provides daily breakfast, lunch, and dinner to his employees, in addition to lodging when they are harvesting and replanting far from home, roofing for their homes when they need it, and registration fees for their children to attend school. Each site employs between 25 to 30 workers and can involve up to 69 families at times.

“It’s a whole community endeavor, and I am pleased and proud that they have an appreciation for what they’re doing and take great pride in it,” said Lozano (oral communication translated by S. King, July 28, 2009). “They know what they’re doing is helping the world.” Lozano added, “The Peruvian Amazon jungle is beautiful, rich, and unique with some of the best biodiversity in the world. Like the lungs of the planet, the Peruvian Amazon absorbs carbon and protects the world.” Besides its use in creating a useful drug, Napo hopes that *C. lechleri* may be planted and harvested in many tropical areas all over the world, which may aid in the removal of carbon dioxide (CO₂) from the atmosphere.

Lozano’s whole family is involved in this business. His daughter works out all the logistics of the paperwork, his brother helps translate paperwork, and his wife supports and helps with everything Lozano does, including cooking for the workers when they need a meal.

“The *Croton* tree has managed to be a source not only of medicine but also a source of jobs for indigenous people and farmers in the rainforest of the Amazonia in Peru,” said Dina Límaco, who also oversees harvesting and replanting sites for Napo. The communities of the workers she oversees have been provided with assistance in building new schools, a football stadium, and a health center, where there is a permanent nurse and a doctor who visits weekly (oral communication, July 17, 2009). Límaco also helps with the little things: “Most of the time they ask for occidental medicine [conventional Western medicine], implements to play football, small motors for their boats, and books and

different things for their schools. But the most important thing we offer them is jobs. This provides a better way of living for them and their children.”

Límaco also noted that the workers are paid according to the appropriate standard set by the Ministry of Work in Peru.

Reforestation and Agroforestry

Napo has assisted in the planting of 317,000 *C. lechleri* trees so far and has established a ratio of 3 to 5 trees planted for every tree harvested.³

Lozano trains and assists workers in building temporary greenhouses, where some *C. lechleri* saplings stay for a few months before being transplanted into an area cleared of weeds. The trees are planted 4 meters apart and checked every 3 months for the first 2 years to make sure no weeds or any plants are crowding them. Once the trees reach 10 meters in height, they are left as is and drained for latex at age 6 or 7 (written communication from C. Lozano, July 20, 2009). The trees grow at a rapid rate of 3 to 4 meters per year, especially during their first 2 years.^{3,14,15}

These trees grow naturally in a large variety of soils, altitudes, and climates, though they tend to occur most frequently near rivers and streams.^{14,15} They also easily propagate through natural germination. After the tree's 5th year, it produces thousands of seeds, for the germination of new *C. lechleri* seedlings. Sometimes those who reforest need to space out these saplings after a certain age for the best results, but other than that, this type of reforestation requires little maintenance.

“Basically you've got a tree that is naturally extremely widespread, abundant, and that grows 1 foot a month in the first 2 years and can easily create other trees,” said Steven R. King, PhD, vice-president of sustainable supply at Napo (oral communication, June 9, 2009), “I wish I could take credit for this, but it was nature that created *Croton lechleri*.”

In 1998, some employees of Napo were involved in publishing an educational manual about sustainably harvesting and replanting *C. lechleri*, of which 5,000 free copies were distributed across Latin America. “El Manejo Sostenible de Sangre de Drago o Sangre de Grado Material Educativo” (The Sustainable Harvesting of the Blood of the Dragon for Commercialization) was reproduced by

the Ministry of Agriculture in Peru, which also distributed thousands of copies throughout Peru.^{14,15} The Agrarian Development Agency of Loreto, Peru, took this even further by creating its own manual, “Cultivo de Sangre de Grado,” which was very close to a reproduction itself.

“They pretty much took one entire section of our manual and reproduced it with very little difference,” said Dr. King, with a laugh. “It was the best example of positive piracy I've ever seen.”

In 1999, a book was published in Spanish explaining the harvesting as well as the value of the tree and its latex: *Desarrollando Nuestra Diversidad Biocultural: Sangre de Grado y el Reto de su Producción sustentable en el Perú* (Improve our Biocultural Diversity: Blood of Dragon and the Challenge of its Sustainable Production in Peru).¹⁶ This book was written and edited by Peruvian forester Elsa Meza, who has done extensive work with *C. lechleri* and indigenous communities in Peru over the past 15 years.

C. lechleri is considered a great candidate for agroforestry, since it grows well with bananas, oranges, coffee, etc., serves as a windbreaker, provides shade, increases the nutrients in the soil, and helps prevent erosion.³ It can also coexist with livestock once it reaches 5 feet in height, which makes it viable for silvopastoral systems, which integrate trees with forage and livestock.

Napo has also replanted 170,000 trees in a buffer zone right outside of the *Parque Nacional Cordillera Azul* (National Park of the Blue Mountain Range) in Chimbaná, Peru.³ Buffer zones are areas that have income-generating activities, such as the harvesting or replanting of *C. lechleri* for Napo, which deter people from reducing the rich diversity of a national park by venturing inside to hunt, collect plants, or harvest primary trees to generate income.

Heart-shaped leaf of rapidly growing, reforested *Croton lechleri*. Photo ©2009 Steven R. King



Quality Control of Sangre de Drago and Distribution

After the harvesting, the latex is poured into 10-gallon containers and transported by boat or car to the quality control/trans-shipment site of the Napo subsidiary companies in Iquitos, Yurimaguas, Lima, and other Peruvian cities. There, it is inspected by a supervisor and, if acceptable, funneled into 55-gallon drums through a filter that will catch any extraneous plant material that might have been accidentally acquired during harvesting.



Collection by volunteers of *Croton lechleri* seedlings for transplant to a temporary nursery for reforestation work.
Photo ©2009 Michael Powers



Croton lechleri trees planted in a secondary forest as reforestation work in Northern Peruvian Amazon.
Photo ©2009 Michael Powers

“It’s a whole community endeavor, and I am pleased and proud that they have an appreciation for what they’re doing and take great pride in it.”



Members of a local community that is collaborating in reforestation process near Chimbana, Peru. Photo ©2009 Steven R. King

The drums are then sealed, and the raw latex is shipped to Glenmark Pharmaceuticals Ltd., one of Napo's partners in Mumbai, India. Extraction and partial manufacturing in Peru is being planned once the crofelemer has achieved US FDA approval.

The latex of *C. lechleri* has a distinctive odor, color, and texture, so it is difficult for anything to masquerade as *sangre de drago*. The latex happens to smell a great deal like barbeque sauce and has a very distinctive taste: "Once you smell that smell and taste that taste, you know what it's supposed to smell and taste like," said Dr. King.

The latex has the look of blood, although perhaps a little browner. If placed on the skin, it tends to cling, although it feels watery at the same time. If a person dabbed *sangre de drago* onto his or her hands and rubbed them together, the latex would first turn to a creamy texture but eventually dry and turn into a fine white powder.

If a shipment passes the quality control tests, the proanthocyanidin compound is isolated, purified, and made into tablets. Currently Napo and its partners Salix Pharmaceuticals, Inc. in Raleigh, North Carolina, and Glenmark are working on the larger scale manufacture of crofelemer. In Peru, Napo is focusing only on replanting at present but will begin harvesting again soon to prepare for mass distribution. The drug is expected to be distributed in India as soon as 2010, and in the United States in 2010/2011, according to Dr. King, depending on how fast some of the regulatory work is accomplished.

Fair Trade

According to Dr. King, Napo is committed to fair trade, sustainable management, and conservation of both tropical forests and the cultural diversity that is a key part of the fabric of Amazonian rainforests. He explained that Napo is committed to ensuring the sustainability of *C. lechleri*.

"A tree called *Cinchona officinalis*, the source of quinine, was heavily harvested, and if seeds had not been smuggled out of the country to be cultivated in Asia and Africa, it would have likely been intensively overharvested," said Dr. King. "Even the famous national tree of Brazil, rosewood [*Caesalpinia echinata*], was nearly wiped out for its perfume, a form of medicine for some. If we overdo it now, this medicine won't exist later, so we thought it best to err on the side of caution." He added, "It's the right thing to do."

It is for these reasons that Napo (when it was previously Shaman Pharmaceuticals) founded the Healing Forest Conservancy (HFC) in 1990. HFC is a nonprofit organization whose mission is to return benefits and profit-sharing to the indigenous people who work with Napo in harvesting or replanting medicinal plants or who have traditional knowledge of the medicinal plants in question.³ Napo also tries to accomplish fair trade through its B Corporation subsidiary Crofelemer Access Program (CAP) Global. CAP primarily works to provide economic alternatives to tropical deforestation in rainforest areas of different biodiversity-rich Andean nations.

"We and our collaborators have tried to always include specific acknowledgement to local and indigenous people and/or authors whenever possible," said Dr. King. "I have been told that they want the world, their children, and future generations to know what ethnomedicine and indigenous science they've provided to the world's medicine



Planted *Croton lechleri* in reforestation site of Cuyana, Peru.
Photo ©2009 Steven R. King

chest. It is an appropriate source of cultural pride and one that has not been properly accorded indigenous people except in general terms—rarely in the medical or scientific community.” HG

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Blood red latex exuding from laticifers of *Croton lechleri*. Photo ©2009 Steven R. King