


From nature to the drugstore

An anti-inflammatory made from the extract of a plant from the Atlantic Rainforest, is ready to go on the market

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The oil from the leaves of the cordia plant (*Cordia verbenacea*) concentrates compounds with anti-inflammatory action



A

plant native to the Atlantic Rainforest, known locally as *erva-baleeira* or *maria-milagrosa*, forms the basis of an anti-inflammatory that had already received clearance from the National Agency for Sanitary Vigilance (Anvisa) and is scheduled to arrive in the pharmacies during this semester. "This will be the first anti-inflammatory remedy made from the extract of a Brazilian plant, the *Cordia verbenacea*", says José Roberto Lazarini, the medicine and research and development director of Aché, the company that is going to launch the product in the form of a cream with the commercial name of Acheflan. "Medicinal plant anti-inflammatory products exist, but they come from other origins such as Africa and other countries." Patented in Brazil and abroad, the new product belongs to the class of phyto-medications, medicines that have within their composition only the active ingredient extracted from plants. By the Anvisa regulations, they can never be mixed with the main synthetic active ingredients, vitamins or minerals. And the same rules applied for the production of medicines must be followed for those of phyto-medications, such as proof of their efficiency and safety. "In clinical tests, Acheflan proved to be efficient and safe for cases of chronic tendinitis and myofascial pain when compared with the main anti-inflammatory on the market, which has as its main active ingredient the diclofenac potassium", says Reynaldo Jesus-Garcia Filho, head of the discipline of Orthopedics at the Federal University of São Paulo (Unifesp) and the coordinator of the university's research program. Myofascial pain has as its most evident symptom persistent muscular pains.

Comparative studies carried out with the cream from *Cordia* and that of the diclofenac derivative that are used in the phyto-medications, resulted in fewer side effects for the patients using the *Cordia* cream such as reddening on the applied location.

"Even being used on skin, we had within the control group (using the diclofenac derivative) a patient with a headache related to the use of this medication and another with a stomach ache, showing that they had significant absorption. In the case of the group using the *Cordia* cream there was no compromising situation of this type", Jesus-Garcia explains. The *Cordia* cream demonstrated therapeutic signs when used

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three times per day. “Within all of the parameters that we analyzed during the comparison between the two medications, among them efficiency and side effects, the *Cordia verbenacea* cream showed a tendency towards improved results, but they were not statistically significant”, Jesus-Garcia Filho says. In order to obtain the necessary statistical comparison, the number of patients will need to be increased.

The idea of turning the knowledge of the fishermen of the São Paulo coast, who for a considerable time had been using the plant to treat bruises and to stanch inflammatory processes, came about from the habit of one of the owners and founders of Aché, Victor Siaulys, of using the *Cordia* after soccer games. He noted that when he has always used the “bottle” — a locally prepared medicinal infusion of the plant — on his sprains and bruises he recovered much more quickly. This verification gave him the incentive to push ahead with the idea of creating a research and development area for phyto-medications within the company in 1989. “As it was something totally new at that time, we encountered many difficulties”, explains Lazzarini.

Proven action - The project went on unsteadily until 1998, when it really got off the ground after a consultation with the pharmacologist João Batista Calixto, a professor at the Federal University of Santa Catarina (UFSC). During 2001 the consultant Luís Francisco Pianowski, a specialist in the area of pharmaceutical technology, joined the group. Together, Calixto and Pianowski discovered that the main active ingredient of the plant, responsible for the anti-inflammatory action was not the one described up until then in the literature, the compound artemetin, of the flavonoids group, but alpha-humulene, a compound of the essential oil. But up until that point its anti-inflammatory effect was not known. “This was the major discovery”, Lazzarini emphasizes. The action of alpha-humulene as an anti-inflammatory was proven both in the pre-clinical tests with mice, and during the clinical tests on humans. In order to produce a

phyto-medication it is not necessary to isolate the main active ingredient, as in the case of allopathic medications.

As one is dealing with a phyto-complex, in many cases with more than fifty substances, not always is it known what is effectively acting on its own and in a group. “In our case, in the tests on animals we could prove that the alpha-humulene was responsible for the anti-inflammatory effect”, advised the medical doctor, Dagoberto Brandão, the owner of Pharma Consulting, a research and development consulting company and the coordinator of the pre-clinical and clinical studies of the new product.



Both the oils of essence and the relevant flavonoids for the medication are concentrated in the leaves of the popularly known *erva-baleeira* (*Cordia*), a shrub mainly found along the coast of the southeast region of the state. The studies relating to its cultivation and the extraction of the plant’s active ingredient, that cover agronomy, chemical and phyto-chemical develop-

ment, were carried out at the Chemical, Biological and Agricultural Research Center (CPQBA) of the State University of Campinas (Unicamp) and coordinated by the researcher Pedro Melillo de Magalhães. “The objective of the agronomy research was to establish a production system on a scale of growing the amount necessary to attend to the production demand”, researcher Magalhães says. An area of the research center in the Paulínia region, close to the city of Campinas, with twelve cultivated hectares of *Cordia* is the guarantee of the provision of the raw material in a quantity sufficiently large to deal with the first phase of the product’s launch.

Within this growing area, every four months the shrubs that are going to be used are cut a few centimeters from the base. From the same cut off trunk, new shoots sprout up and so on successively. The offshoots of the *Cordia* planted at the start of the project are still producing in the field.

The extraction of the essential oil, the raw material necessary for the laboratory to make up the final formula, is also done at the research center of

Unicamp, which has a supply agreement with Aché. Biological markers guarantee the quality and consistency of the extract, which cannot have variation in order to guarantee the standard of the raw material. “There can’t be any variation in the concentration of the principal active ingredients, all of them have to be the same as before”, says Brandão. Standardization is one of the demands of an Anvisa resolution, dating from March of 2004, for the production of phytomedications. And this resolution has as its objective to control both the vegetal raw material and the medications themselves. In the clinical tests a standardized extract equivalent to that which is going on the market was used.

With agronomists, biochemists, pharmacologists and medical doctors, there have been more than one hundred professionals involved with the project between 1998 and 2004. The pre-clinical studies involved pharmacological and toxicological tests in laboratories and afterwards with mice. “The clinical research was carried out at university centers and followed the rigorous directives of the National Health Council and those of Anvisa”, Brandão emphasizes. The clinical tests were done in three stages, with the participation of almost 700 patients. During phase 1, the product was tested on around 270 healthy volunteers, in phase 2 around 90 patients suffering from chronic tendinitis and from myofascial pain and in phase 3 there were approximately 280 patients with the same illnesses. Similar studies were carried at the Orthopedics Department of Unifesp and at the Medical Faculty of the Catholic Pontifical University of Campinas (Puccamp).

After having complied with all of the stages of pre-clinical and clinical testing, Aché sent off a request for registration to Anvisa, approved in November of last year, to use Acheflan in cases of tendinitis and myofascial pain. Now the laboratory is researching the use of the extract in the form of a pill for the same ailments. And also, is beginning to study the use of *Cordia* for osteoarthritis and physical traumas. During the seven years in which the project was taken forward without interruption, the Aché company has in-



Plant extract (above) and the growing area in Paulinia

vested more than R\$ 15 million in the research and development of this phyto-medication. The company, which last year had a gross income of R\$ 900 million, has annually applied R\$ 10 million in the research and development of new products.

Billionaire market - For now, the launch of Acheflan is restricted to the national market, which moves around R\$ 400 million per year only with phytotherapeutic medications. Some phytotherapeutics that are on sale, such as teas

and capsules of natural products, do not fit into the category of medicines and for this reason they do not enter into this calculation. Abroad, this segment tallies up to US\$ 21 billion per year. For this reason, conquering a slice of this billionaire market is one of the company's goals. "We have been in conversation with possible partners in Europe and the United States and we have various of them interested", says Lazzarini. "We are now in the phase of evaluation."

The company has other eight phyto-medication projects, but they are not saying what they involve as the patents are not yet registered. In order to develop the projects in

this area they created a division called Phytomédica, which has presented as its first research and development result a product indicated for the treatment of the symptoms of post-menopause based on isoflavons of soya, often used in China, from where it originated, as well as Japan. Nevertheless, the new phyto-medication was made from a Brazilian plant. The research was totally carried out in Brazil, right from the agronomy, chemical and phyto-chemical studies to the formula of the final product. "The interesting fact is that it sprung up from an idea that went well", says Jesus-Garcia Filho. ●