

SANGRE DE DRAGO

THE BLOOD OF THE FOREST

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Sustainable Exploitation

We have been hearing nothing but this all over the world, and in the south of the world in particular, for about the past 20 years.

These two words have become a sort of magic formula without which it is inconceivable of taking on any project for production.

At least in theory, because the reality is very different.

According to the merciless data provided by TRAFFIC, the WWF agency that monitors the trade of medicinal plants in Europe, 89% of medicinal plants are collected in their wild state without great concern being shown for the ecological damage caused to the environment.

Only 11% come from cultivated areas (Lange 1988).

In Italy in particular, there exists a preferential relationship between our companies and some countries, principally Albania, the largest supplier of medicinal plants (data presented by the Higher Institute for Health on 7th March in Rome).

There would be nothing wrong here except that the standards of quality of agriculture in this country, depleted uranium aside, are the lowest in Europe and the directives in the ecological sector are virtually nonexistent.

And yet in some cases, nature takes her revenge, by imposing precise limitations on companies' commercial prospects.

This is the case of the Amazonian tree Sangre de Drago, the latex of which is the most powerful natural cicatrizing known today.

Its active ingredients have been studied in detail by the pharmaceutical industry, but their chemical synthesis cannot currently be proposed: on the other hand, the only possibility for large-scale exploitation of this natural product is via the techniques of sustainable agricultural and forestry production.

Otherwise, with an average production per individual of about two litres and the subsequent death of the tree, the resources currently available in Amazonia would soon be exhausted.

Ethnobotanics

First of all, we must clarify one thing: the term "Sangre de Drago" indicates today at least three species, coming from different parts of the world.

There exists a "Sangre de Drago de Sumatra", which can be identified botanically as *Daemonorops draco* (Will) Blume and a "Sangre de Drago de Socotra", which corresponds to *Dracaena cinnabari* Balf. F. The former is the latex of a palm whilst the latter is the sap of an Agavaceae. Both are used exclusively as colourings.

Apart from these "false" "Sangre de Drago", on European and American markets "Sangre de Drago" refers to the latex of a member of the Euphorbiaceae family, which can be botanically traced back to a limited number of species of the *Croton* genus: *Croton lechleri* Muell Arg, *Croton draconoides* Muell. Arg, *Croton palagnostigma* Klotzsch. In addition to these three species, mention should be made of the *Croton cajucara*

Benth and the *Croton urucurana* Baillon, a Brazilian species used in ways partially overlapping with those of the previous species, although with a phytochemical profile which is only partly the same.

It has been used for thousands of years by the indigenous populations of Peruvian and Ecuadorian Amazonia as a cicatrizing and hemostatic, for both external and internal use. When the Spanish arrived, the indigenous remedy must have immediately attracted the attention of the colonial doctors, partly because of its efficacy and partly because it perfectly fitted in with the "theory of signatures" according to which any red-coloured liquid from a plant had to have something to do with blood, so much in vogue at the courts of Europe of that period. Hence the name "Sangre de Grado" or "Sangre de Drago": the "dragon" in popular mythology is the great spirit of the Amazonian forest, often imagined as an enormous snake by the natives and transformed into the mythical dragon of the colonial imagination.

In general they are trees between 10 and 20 metres in height, with a trunk of 15-25 cm. in diameter. The bark is greyish-white in colour and when cut, an intense red resin flows out. The leaves are 12-20 cm. long and 5-14 cm. wide, often reddish in colour and tomentose on both sides. The inflorescences are grouped in small branches more than 30

cm in length. The fruit is a globular depressed capsule, about 3mm long and up to 4.5 cm. wide.

Phytochemistry

From the phytochemical point of view, the active ingredients of "Sangre de Drago" belong to three main categories.

The surprising thing is the profound synergy of action of these components, to the extent that they are often quoted, as rare documented examples, even in the most critical reviews (Williamson 2000).

Fundamentally, three fractions are involved. An alkaloid fraction, represented mainly by taspine.

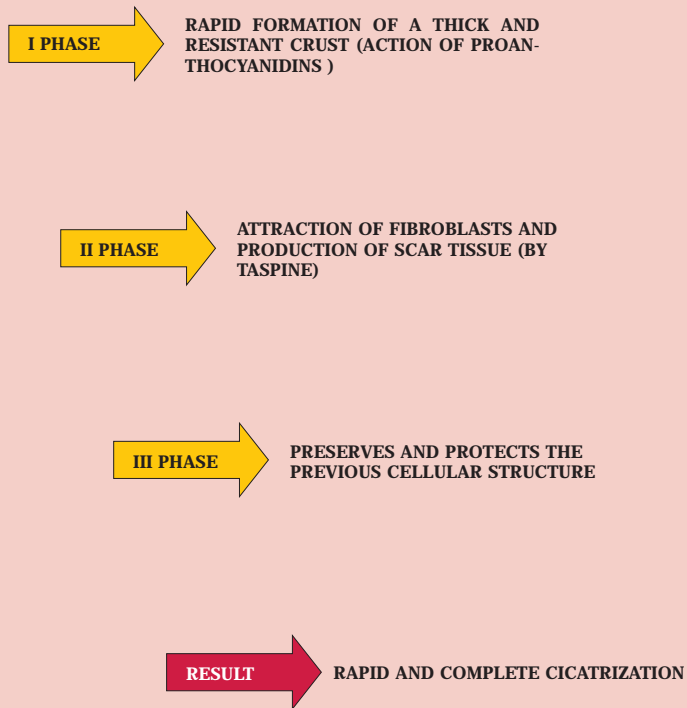
This alkaloid possesses in vitro cytotoxic activities on V-79 cells (Itokawa et al. 1991) and KB cells (Chen et al. 1994) and anti-inflammatory activities in the tests on oedema from carageenan in a rat's foot, granuloma induced by a ball of cotton and polyarthritis by adjuvant (the three classic animal models on inflammation) (Persinos Perdue et al. 1979).

But taspine acts above all on the cicatrizing process reviving the fibroblasts, the most important for the production of new repairing tissue. In addition to this fraction, Sangre de Drago also contains two other types of substance: proanthocyanidins responsible for the rapid cicatrizing action of this latex, which can represent up to 90%

of the dry weight (Cai et al. 1991) and a fraction consisting of lignans of the diterpene type, the action of which in part is complementary to that of taspine (Cai et al. 1993, Pieters et al. 1993).

Pharmacology

Undoubtedly the most important activity of Sangre de Drago is the cicatrizing activity and the fundamental characteristic of this product is its speed of action. This seems due mainly to the action of the proanthocyanidins, the complex structure of which would appear to induce an immediate precipitation of the serum proteins, probably due to a physical rather than chemical action, with the formation of a thick and resistant crust. In the animal models on which experiments were carried out, this was reached in extremely reduced periods of time, less than 24 hours (Pieters et al. 1995)! Overlapping this first action is that of taspine, in the past considered to be the main cicatrizing ingredient of Sangre de Drago (Vaisberg 1989). Today, it seems that its activity mainly consists of attracting the fibroblasts to the place of the lesion, encouraging the production of new scar tissue (Porrás-Reyes B. et al. 1993). Alongside the action of taspine, the action of the lignans is of special interest, such as 3',4'-O-dimethylcedrusine, capable of preserving the



original tissue, as shown by the tests of incorporation of tritiated thymidine in the endothelial cells (Pieters L. et al. 1992). The fundamental characteristic of Sangre de Drago is, as we mentioned above, its speed of action. This has certainly made the product extremely useful for the indigenous populations of the Amazonian forest, where the threat of microbial contamination of injuries is a real and dramatic danger. In our urban environment, this property may appear excessive: the utility of Sangre de Drago is therefore to be found in all those lesions of a chronic nature, which for various reasons heal with difficulty, for example, decubital ulcers, diabetic ulcers and, above all, erosive gastritis and ulcers of the gastrointestinal tract. It is however surprising to note how, despite these indications, the majority of the technical data available to date on the gastroprotective activity of Sangre de Drago concerns above all the Brazilian species rather than the Peruvian ones which are present mainly on European markets. In this case too, studies have mainly been carried out on animal models. *Croton urucurana* has shown an anti-microbial activity towards *Staphylococcus aureus* and *Salmonella typhimurium* (Peres et al. 1997), and an analgesic and anti-inflammatory activity (Lopes Pereira Peres et al. 1998). As far as *Croton cajucara* is concerned, it contains two

active fractions: essential oil and diterpene compounds. The essential oil, obtained from the bark in a concentration of 1%, is capable, at a dose of 100 mg/Kg⁻¹, of significantly reducing ulcers of the gastrointestinal tract in rats induced by hyperthermic stress (48%), by indomethacin (47%), by ethanol (86%) and by ligature of the pylorus (87%) (Hiruma-Lima et al. 1999b, Hiruma-Lima et al. 2000). In addition to this activity, the essential oil of *Croton cajucara* has shown an anti-inflammatory and analgesic activity (Bighetti et al. 1999). Of the diterpenes, dehydrocrotonin has been isolated. This substance has been capable of modifying the gastric pH and the concentration of acids and inducing the release of prostaglandine-2 from the cells of the gastric mucous (60% greater with respect to the control) (Hiruma-Lima et al. 1999a), showing a considerable anti-ulcerogenic activity in the animal models (Souza Brito et al. 1998). This is associated with a hypoglycemic action, shown in rats in which diabetes had been induced by administration of alloxan (Farias et al. 1997) and an anti-estrogenic activity (Luna Costa et al. 1999). Lastly, the polyphenolic fraction of Sangre de Drago contains compounds with an anti-viral action, which have shown considerable in vitro activity against the Herpes Virus (Barnard et al. 1993) and when

administered by aerosol against the influenza A virus of syncytial pneumonia (Gilbert et al. 1993; Sidwell et al. 1994)

Clinical Tests

Clinical tests on Sangre de Drago are limited to three specific sectors: infections from Herpes Virus, diarrhoeas of viral origin and an open study on its topical use in the case of insect bites. In the first case, two tests have been carried out on an ointment containing a polyphenol of Sangre de Drago, named SP-303. This was an open study on 9 subjects, affected by AIDS with acyclovir-unresponsive monocular herpes simplex. After 14 days of treatment, the study shows an improvement in the lesions of 3 subjects, worsening in three other cases and a substantially unmodified situation in the other three cases. However, it must be underlined that these were subjects who were strongly compromised from the immunity point of view (average values of CD4: 7), in a terminal state of AIDS (Safrin et al. 1994). Another double-blind randomized test was carried out on 46 subjects, affected by AIDS and with genital lesions from recurrent herpes virus. The test showed complete remission of the symptoms in 41% of the subjects (9/22); the conclusion, on the basis of these results, was that this ointment, based on SP-303,

did not represent a valid alternative to the administration of acyclovir by mouth. This is the elected drug in the treatment of infections from herpes virus and the only one that has shown a significant efficacy, even if at the cost of a certain frequency of collateral effects. The clinical result of this test was, on the other hand, comparable to that obtainable with acyclovir ointment which today, to all effects, is considered a no more effective treatment than a placebo (Orozco-Topete et al. 1997).

As far as viral diarrhoea is concerned, there are two tests on Sangre de Drago: one on 51 subjects, affected by AIDS with CD4<200, affected by symptomatic diarrhoea. Through the culture test, pathogens are not shown which testify to a probable viral etiology. A double-blind randomized test was carried out against a placebo. The group treated showed a significant decrease in the number and quantity of faeces produced compared to the placebo group (Holodny et al. 1999). The mechanism of action can probably be attributed to an action on the cyclic CAMP mechanism, which regulates the flow of ions (especially Cl⁻) in the gastrointestinal membrane and therefore the presence of liquids inside the gastrointestinal tract (Gabriel et al. 1999). This way, the mechanism of action of the compounds of Sangre de Drago does not appear to be in relation with the

etiology of the disease but rather with the physiological mechanisms of the genesis of the diarrhoea and would therefore also be valid with different causes.

Another test on 184 travellers in tropical countries (Mexico and Jamaica) has shown a complete remission in 90% of the subjects, who took Sangre de Drago and were affected by travellers' diarrhoea, in less than 24 hours against the 29.3% of the subjects in the placebo group. The result was highly significant. (Di Cesare et al. 1998). Moreover, Sangre de Drago, in its natural form, had also shown a marked activity of the necrotizing enterocolitis (Miller et al. 2000).

These results are probably to be attributed to the powerful cicatrizing action of Sangre de Drago, as confirmed by the excellent results obtained on insect bites in agricultural workers engaged in pesticide diffusion (Miller et al. 2000).

On the basis of these results, Sangre de Drago has been successfully proposed as a topical preparation for insect bites in children.

Safety

Sufficient data exist in order to state that Sangre de Drago is a preparation which has been traditionally used for a long time and for which clinical tests have shown a sufficient margin of safety and efficacy. The interpretation of some in

vitro data is more problematic, according to which Sangre de Drago would appear to be anti-oxidant in high doses and pro-oxidant in low doses (Desmarchelier et al. 1997).

Moreover, the same group of researchers has disproved this data showing how this natural product has a considerable protective activity against peroxidation of lipids, even in low doses (Desmarchelier et al. 1999).

Sustainability

As we said at the beginning, sustainable production is the keynote to be faced by any company intending to put products based on Sangre de Drago on to the market. A large part of the data available today is based on the work carried out by two companies, one Italian and one American, and can therefore be traced to the particular type of exploitation followed by them. Their work however presents some points in common that allow us to have some fundamental data. The density of *Croton lechleri* in the area studied (forest of Tarapoto, Aguaytia, Pucallpa and Atalaya in Peruvian Amazonia) is of 13-15 individuals per hectare, even if there exist areas with a density of up to 90-150 individuals/hectare. It is a typical pioneer species (which grows quickly in areas of deforestation) for which 100-400 trees/hectare can be reached with appropriate forestry methods. The seeds are

generally cultivated in nurseries and then transplanted when they reach a height of 25-35 cm. There exists however a good level of spontaneous dispersion of the seeds: a laurel can produce up to 600,000 seeds per season, which are dispersed by the wind, birds and other animals.

Consequently, spontaneous regeneration is fairly high. The growth of this species is fast: 30-40 cm. a month, throughout the whole year.

From the sixth or seventh year (when the tree attains a diameter of 25-27cm) it enters the productive phase: each individual generally produces 2-3 litres of latex, after which it dies.

The two companies agree that it is substantially pointless to look for other forms of sustainable extraction: the tree from which the latex has been removed is nevertheless doomed to die in time. In view of the speed of growth of the species and the possibility of intensive forestation, it is just as worthwhile to cut down all the trees that are to be exploited and extract the largest quantity possible of latex, subject obviously to a sustainable plan of reforestation. All the main institutions are now in agreement on this position and, after having identified in this species one of the promises of the future Amazonian economy, on the basis of these data and the tests mentioned above, have embarked on major plans of commercial exploitation.

The ITTO (International Tropical Timber Organization – an organization linked with the UN) has begun the reforestation of more than 82,000 trees in the Ucayali, whilst the Peruvian Ministry of Agriculture is financing the reforestation of more than 2,000,000 trees (400,000 of which in the region of Iquitos alone, to date excluded from the trade of this species). A good outlook for those who have at heart not only the quality of products but also the fate of the environment.

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