ANTI-MALARIAL REMEDIES FROM CLASSIC CHINESE PHARMACOPOEIA

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"All art is but the imitation of nature"
Lucio Anneo Seneca

Out of the 248 thousand species of plants existing in the world, only a small percentage has been studied[1]. Amazonia, the Andes, Borneo, India, China, the Philippines and Africa: this is where the huge unexplored pharmacy created by Mother Nature is to be found to a great extent. There have been two fundamental stages in the current renewed interest in ethnopharmacological research. In 1960 the American Cancer Institute launched a study on a vast scale. Thousands of plants were taken to the laboratories and studied. The result: sixteen years later, researchers had identified only two useful active ingredients. But the study had been conducted absolutely by chance. In 1960 the American National Health Institute started a five-year plan, this time with a target. Thousands of researchers were invited down, into the world below. Patiently and humbly, they questioned witch doctors, shamans and curanderos. And they only tested the plants that were already part of medical traditional, however different and fanciful they may have been. The result: in five years, about twenty useful active ingredients were identified. It would have been sufficient to identify only a couple to amortize the costs of the study. The road must genuinely have been interesting and promising, as about three-quarters of the plant-based drugs used today derive from remedies already known to native medicine. In the meantime, something new was happening in the West, regarding politics, the economy, science and customs[2]. The Incas cured "Dengue fever" with the bark of the quinquina tree. The active ingredient, quinine, was not isolated by chemists until 1820 and is still essential against malaria. In the early 19th century, the chemists tried to isolate the active substance of the drug and in 1820 Pellentier and Caventou discovered the alkaloid Quinine, for the synthesis of which it was necessary to wait another century (Rabe, in 1929). Intravenous administration of quinine, is still our most effective arm in the treatment of serious malaria, quickly leading to an elimination of the parasitemia and lowering the temperature. The most frequent side effects are known as cinchonism (nausea, headache, dizziness, visual and hearing disturbances) In some cases a permanent loss of hearing can be observed. Quinine stimulates the ß cells of the pancreas, inducing hypoglycemia, and especially when used parenterally it must be accompanied by intravenous administration of glucose, with close monitoring of the blood glucose values. It is contraindicated in patients with cardiac disturbances and should not be used in digitalized patients or patients in therapy with warfarin. The first cases of resistance were reported as early as 1910 in Brazil. It has been seen however that resistance to quinine disappeared when the pharmacological pressure was lowered. At present, we find resistances of type RII and very rarely of type RIII in Cambodia, South Vietnam and in some areas of Thailand. Until the discovery of cloroquine, it was the main drug in the treatment of malaria. There is room for it once again where resistance to Cloroquine has developed. Quinine is a powerful schizonticide of the blood which is against all four species of plasmodium. It is an erythrocyte drug and does not have an effect on the hexo-erithocyte or gametocyte. Its mechanism of action is similar to Cloroquine and it also interferes with the DNA of the parasite. It is well absorbed by the intestine. 80% bonds with the plasma proteins, the half-life is of 10 hours and it is metabolised by the liver and eliminated with the urine in 24 hours[3]. In 1972, Chinese scientists succeeded in extracting a sesquiterpene lactone from the plant of Artemisia annua (qinghao), mentioned for the first time in 168 BC in the Chinese text "Remedies for 52 diseases", discovered in the tomb of Mawangdui Han, in Changsa, in the province of Hunan. In this text, Artemisia annua was described as a remedy for haemorrhoids. The first certain reference to the use of the plant against malaria dates back to 340 AD, when it was mentioned by Ge Hong in his "Prescriptions for Emergencies"[4]. Its schizonticide action is fast and also appears with the resolution of the clinical situation in a short time [5]. It appears that it also has an effect against the gametocytes, whilst it does not act against the pre-erythrocyte forms. Its structure and its mechanism of action are different from the other drugs, therefore, in the absence of pharmacological pressure, resistance has not yet been found[6]. Administration can be oral, intramuscular, intravenous and rectal. To avoid relapses and counteract the onset of resistance, a therapeutic cycle with Artemisia is generally associated with mefloquine from the second day of treatment, having already obtained the elimination of the parasitemia and increased tolerability to mefloquine[7]. This type of drug, associated with lumefantrine, a racemic compound of fluorene, is indicated for the treatment of malaria, including the treatment with over the counter drugs for emergencies of adults and children with infections due to P. falciparum and infections mixed with P.falciparum[8]. Artemisia/lumefantrine is not yet available in Italy, whilst the authorization for commercialisation has been given in Switzerland. This drug rapidly removes the parasites with a low percentage of recrudescence and rapidly eliminates the symptoms associated with malaria, for example: fever, nausea, vomiting, fatigue etc.; it has a gametocide activity which can potentially reduce the transmission of the infection, it counteracts the disease progressing to cerebral malaria, it is effective in areas with resistance to the drugs and has a good tolerability. The dosage depends on the area of exposure but it is based on a single combination of tablets of 20mg of artemisia and 120mg of lumefantrine. The drug has been developed jointly by Chinese researchers of the Institute of Microbiology and Epidemiology of Beijing and a European company, which holds the rights of commercialisation at worldwide level, outside the People's Republic of China [9].
Today, resistance to the drugs against malaria is emerging which is spreading quicker than new medicines can be developed. Considering the speed with which the parasites are becoming resistant and the time necessary to develop new drugs (from 5 to 10 years after the clinical discovery), there exists an evident crisis: malaria becomes resistant to multi-pharmacological treatment and there are no effective alternatives. The national protocols to treat malaria include first line treatment and second line treatment. First line treatment is for simple malaria. Second line treatment is for serious or complicated cases of malaria and is used when the first line treatment does not work. In Africa the national protocols of treatment recommend in general the use of a classic antimalarial (such as cloroquine or Fansidar) as first line treatment. But in recent years, resistance to these drugs has considerably increased. Experts now recommend a change of protocol to include a combination of antimalarial drugs. The combinations, thanks to their capacity to affect different biochemical targets of the parasite, are more effective and allow reducing the length of treatment. The active ingredient of Artemisia annua has not determined, in centuries of traditional use, any form of resistance [11] [12]. A very recent study published in the journal "PLoS Medicine"[13] suggests that the combined therapy based on derivatives of artemisinine (a class of anti-malarial drugs) may not be the ideal treatment for cases without complications of malaria in Africa. On their own, the artemisinine derivatives can cure the most serious types of malaria (falciparum malaria) in seven days. However, without a combination with other drugs, there is a strong risk that the disease will reappear. The artemisinine derivatives can also slow down the development of resistance to other anti-malarial drugs. But the combinations of these drugs are fairly expensive, and to date little experimentation has been carried out in the areas where the malaria is most frequent. In a randomized trial conducted at four sites in Uganda, the researchers led by Grant Dorsey of the University of California of San Francisco have shown that a combination of more economic drugs – amodiaquine and sulfadoxine-pyrimethamine – succeeds in impeding recurrent infections of malaria in patients at least to the same extent as combinations based on artemisinine derivatives. In sites characterized by the highest rates of transmission, the cheapest combination also works better. Although the combinations of artemisinine derivatives are very promising, the authors conclude that the ideal regime has not yet been determined and that cost represents a serious problem. Wider and longer experimentation will be necessary in very different conditions, to compare the efficacy of the different therapies.

Part of Exegetic Tantra, Chapter 20, "Herbal medicines". By courtesy of "Antica Medicina Tibetana", Zanfi Editori

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