From the history of medicinal plants: cinchona tree

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SUMMARY

Herbal raw materials as the most ancient medicine appeared in human life from the moment of his formation as a rational being. The stories of many types of medicinal plant materials are inextricably linked with the history of medicine, with the fight against many serious diseases. The fight against malaria has become one of the most difficult problems in medicine. The cinchona tree gave mankind the ability to effectively fight this disease. The article examines in the historical aspect the appearance in the arsenal of medicine of such a drug as quinine, which in our 21st century has not lost its significance.

Key words: malaria, cinchona, Cinchona sp., Cinchona alkaloid, quinidine, quinine, artemisin.

RESUME

In modern medicine herbal medicines occupy a significant place. These ancient medicines have come to scientific medicine from traditional medicine of various regions of the world. Some medical plants are currently the only raw materials for valuable medicaments: cardiac glycosides, alkaloids and etc. Most of them have a difficult and interesting way from traditional medicine and scientific medicine to inculcation to a wide medical practice. One of them is cinchona which allowed mankind to fight with malaria. The article contains little-known historical facts about appearance, research and inculcation into medicine a valuable medicament - quinine which saved millions of lives.

Keywords: malaria, cinchona, cinchona bark alkaloids, Cinchona sp., quinidine, quinine, artemisin.

In the world of medicines, herbal preparations occupy a special position. These ancient medicines appeared in the life of a person from the moment of his formation as a rational being. To survive in the wild, man had to not only get food for himself, including plant food, but also to find plants that would alleviate his condition in case of various diseases. Through trial and error, people have learned to find plants with healing properties in the world around them. Thus, mankind has accumulated rich experience in the use of plants as medicines for many millennia. Medicinal plants have been widely used and are currently used in folk medicine in various regions of the world. As the study of the chemical composition and pharmacological properties of medicinal

Plants were gradually included in the list of medicines in scientific medicine. And at present, herbal preparations occupy about 40% of the pharmaceutical market [3].

Almost every medicinal plant has its own interesting path from traditional to scientific medicine and introduction into widespread medical practice. One of these plants is the cinchona tree, which has given humanity the opportunity to fight malaria.

The purpose of this work is an information and analytical study on the use of raw materials and preparations of cinchona in medicine in a historical aspect.

Malaria - one of the most difficult problems in medicine appeared more than 10 thousand years ago. Its occurrence is associated with climate change and the formation of many lakes where mosquitoes could breed.Anapheles, whose female iscarrier of the parasite of the genus Plasmodium causing the disease. Descriptions malaria as a disease with characteristic febrile attacks appeared in the medical literature during the Middle Ages. The wide spread of this disease throughout the world, millions of cases and deaths give reason to consider malaria as the most serious parasitic disease. Despite the tremendous advances in medicine, millions of people are sick with malaria in the modern world, and hundreds of thousands die. It took several centuries for scientists of different specialties to comprehensively study this disease and develop drug methods for its treatment and prevention.

One of the first drugs effective in the treatment of malaria was the alkaloid quinine, isolated from the bark of trees of the genus Cinchon or cinchona tree (Cinchona L.) of the madder family - Rubiaceae [nine].

Back in the late 30s of the 17th century, Jesuit monks from Lima noticed that the Peruvian Indians successfully used the powder of the bark of a tree called "guina-guina" to treat fever, and reported this in Rome. Cardinal Juan de Lugo was instructed by Pope Innocent X to collect all the information about the healing bark. After the court physician Gabriel Fonseca studied the effect of decoction of bark in the treatment of a three-day fever, Cardinal de Lugo launched an extensive campaign for the use of cinchona bark, then better known as "Jesuit powder" or "cardinal powder". However, the results of this campaign were very modest.

Nobody could explain what the words "guina-guina" mean. They were associated with the meanings "bark" or "clothing". Doubling the root of the word in South America expressed special respect, thereby emphasizing the high value of the plant. In Europe, not understanding this Indian word, they began to change it in every possible way, as a result, and got china (china) and, accordingly, “cinchona tree” [6].

In the 70s of the XVII century. London doctor and pharmacist Robert Talbor used a "secret remedy" in his medical practice - some kind of powder. In 1670 R. Talbor used this remedy to treat the English king Charles II. And a little later, with his help, he cured the Dauphin, the son of the French king Louis XIV. The king bought the secret of the drug used from the doctor for a fabulous sum - 48,000 livres. Secret remedy turned out to be bark powder

cinchona tree. In 1672 R. Talbor published a pamphlet "Ryretologia, arationalac count of the cause and cureofagues", in which he describes the use of cinchona bark for the treatment of fever and warns readers of the dangerous effects of its incorrect use.

The malaria epidemic captured more and more countries. The causative agent of this disease was not yet known, and the main characters did not appear on the scene - the Indian doctor and parasitologist Ronald Ross, the Nobel laureate, which he received for his work on malaria, the Italian Giovanni Batista Grassi, the entomologist and parasitologist, the French physiologist Charles Louis Alfon Laveran, Scottish parasitologist Patrick Manson, Russian professor D.L. Romanevsky, who did a lot to investigate the nature of malaria and find ways to combat it. Peruvian bark powder remained the only active drug, despite ongoing controversy among doctors about its effectiveness.

It was almost impossible to get a healing agent - the local Indians sacredly kept the secret of collecting bark, and the trees themselves tried not to show them to strangers. The long and tragic history of the cinchona tree contains many names of courageous people who gave their lives for trying to penetrate the thicket of tropical forests. Among them can be called the French botanist Bernard de Jussieu, who in the 18th century for 17 years, studying the rain forests in the highlands of South America, bit by bit collected information about the Peruvian tree. And only the French scientist Charles Marie de la Condamine, during scientific expeditions to South America in 1736, first saw the evergreen cinchona tree in the Loja Valley. The scientist was delighted with the beautiful silvery bark on a mighty stem, shiny leathery leaves and light crimson flowers gathered in panicles, reminiscent of lilac brushes. Sh.-M.Chinchona) [12].

There are several versions of why it was named that way. According to one of them, the tree was named after the Viceroy of Peru, Don Luis Geronino Cabrera de Vabadilla, Count Chinchon. As soon as he reached the coast of Spain, exhausted from the fever caused by malaria, he immediately handed over the most expensive cargo to the best doctors in Madrid - a package with the bark of a Peruvian tree. But European celebrities were unable to unravel the secret of the mysterious bark and save Count Chinchon from death. According to another version, all this happened to the wife of the Viceroy of Peru, Countess Ana del Chinchon (Chinchon). The Latin name for cinchona was written earlier as Chinchona, only in 1866 The International Botanical Congress decided to change the spelling of the plant name to a more euphonious - Cinchona [3].

It was difficult to establish the active principle of the bark of the cinchona tree, which lasted for several centuries. The idea of extracting pure substances from plants has occupied the minds of scientists since the time of Paracelsus. Following the path indicated by the works of the Swedish pharmacist Karl Scheele, the French researcher Antoine François Furcroix in 1791 isolated a crystalline substance from the bark of the cinchona, which decomposed when heated to form ammonia and had, like the bark itself, a very bitter taste. But unfortunately,

the scientist did not complete his experiments and did not give a complete description of the substance obtained. And although Furcroix was firmly convinced that he was able to establish the active substance of the cinchona tree, there are still disputes in the scientific world about which compound the French researcher isolated from the bark of the cinchona [4, 7].

The chemical study of the cinchona bark continued. In 1811, the Portuguese Bernardino Antonio Gomes, a physician, chemist, botanist and parasitologist, obtained from cinchona a crystalline substance with all the properties of alkaloids, and named it cinchonine. However, in 1820, the French chemists Joseph Pelletier and Joseph Cavent proved that B.A. Gomesh cinchonine was actually a mixture of two alkaloids, which they called quinine and cinchonine. Immediately after the isolation of alkaloids, J. Pelletier sent them away to François Mozhandi, who, in animal tests, showed that the antimalarial properties of the plant were due to quinine. In September 1820, scientists made a report at the Paris Academy of Sciences about the discovery of the main active ingredient of the cinchona bark. Immediately after the report at the Paris Academy, the doctors Double and Shomel, having tested the allocated quinine on the patients,

For another 16 long years, quinine did not find recognition among doctors. Even the awarding of J. Pelletier and J. Cavent in 1827 by the Paris Academy of Sciences of the national prize of 10 thousand francs "for an important achievement in medicine" could not shake the prejudice towards quinine in medical circles. Only the courage and desire for innovation of the young French military doctor Mayo helped to convince the doctors. While in the active French army in Algeria and convinced of the ineffectiveness of bloodletting - a generally recognized method at that time for the treatment of malarial fever, which suffered a large number of soldiers, the young doctor decided to try the "rejected" quinine. The very first tests gave an excellent result, and soon quinine was widely used in all French military hospitals in Algeria.

In 1900, with funds raised by the public from different countries, a monument to the discoverers of quinine J. Pelletier and J. Cavent was erected in Paris. At its opening, the director of the Higher School of Pharmacy, in which both researchers once worked, said: “Science also has its own book, in which history records victories won. These victories are not worth tears to any people, but on the contrary are a boon for all. And if we judge the significance of these victories by the number of people saved from death, then the names of Pelletier and Cavent should be written in this book in the most honorable place. "

As pharmacists, J. Pelletier and J. Cavent sought to find practical application for their discovery, which made them start producing quinine. In 1826, 1800 kg of quinine sulfate from 138 tons of cinchona bark were obtained in their production workshop. By making their discovery available to the public, scientists gave everyone the opportunity to use it. Thanks to this, German entrepreneurs started to produce large-scale quinine according to the Pelletier-Cavent method. North American colleagues did not lag behind them [8, 9].

The discovery of quinine was viewed by contemporaries as the beginning of a new era in the development of medicine, instilling confidence in a favorable outcome of treatment. And if earlier, when using a decoction of the bark, the doctor was forced to act, to a certain extent, blindly, not knowing the exact activity and dosage of the decoction, now, when using a pure active substance, the possibility of accurate dosing has appeared.

The bark of the cinchona tree was in great demand, and the production of quinine turned into an entire industry. Cinchona has a very limited natural distribution: trees grow wild only in Peru, Bolivia, Ecuador and Colombia, on the eastern slopes of the Andes, at an altitude of 1600–3200 m, without forming continuous thickets. It was easier and more profitable to remove the bark from a tree that was felled. For this reason, by the end of the 18th century, about 25 thousand trees were cut down in nature every year, and by the middle of the 19th century. there was a danger of the complete destruction of the tsinkhona. A method for obtaining synthetic quinine had not yet been found; it was necessary to look for other solutions, namely, to introduce the tree into culture. In his homeland, Peru, there were no enterprising organizers, therefore, it was necessary to grow the cinchona tree outside the Amazon River basin [9–12].

The profits from the sale of bark were so great that the governments of Bolivia, Peru, Colombia and Ecuador, in an effort to maintain their monopoly on the sale of valuable medicinal plant materials, banned the export of both whole plants and cinchona seeds. However, in 1853, Karl Justus Husscarl, director of a botanical garden on the island of Java, managed to secretly take out of South America the seeds of cinchona kalisaya -Cinchona calisaya. Trees on about. Java goodgrew, but to the chagrin of all Dutchmen, the bark of this type of cinchona contained very little quinine. The same story happened with the British, who planted the stolen seeds of pubescent cinchona in India and Ceylon -Cinchona pubescens.

In 1861, the Australian Charles Ledger, who was involved in the extraction of bark in South America, with the help of the Indian Manuel Mameni, who worked with him, persuaded the Bolivian Indians to sell him some seeds of a tree, with the bark of which they treated fever with great effect. Charles Ledger wanted to sell the seeds to the British, but the British government rejected his offer because it no longer believed in the success of such an event. Only 1 pound of seeds for about $ 20 was purchased by the Dutch government, and the purchased seeds were sown on about. Java. This deal was recognized as the most successful in history, because it turned out that the content of quinine in the bark of trees grown from these seeds reached 13%. The grown plant was named the Ledger tsinkhona -Cinchona ledgeriana [3].

It took many years of work to master the culture of tsinkhona and increase the alkaloidity of trees through selection. Over time, the export of cinchona bark from South America began to gradually decline. In the early 30s of the twentieth century, 95% of quinine was obtained from the bark of trees from plantations on the island. Java, which brought great profits to the Dutch. Currently, extensive plantations of cinchona are found in India, Indonesia, Africa, South America. Two types of cinchona are most widely cultivated: red-juice (Cinchona succirubra) and Ledger.

Depending on the species, age of the plant and the place of growth, the content of alkaloids in the bark can vary from 5% to 17% [5, 6].

In Russia, repeated attempts to introduce the cinchona tree into culture were begun at the beginning of the 20th century. in the Batumi Botanical Garden, but the plants died in cold, frosty winters. A new direction for the culture of the cinchona tree was given by the work of Soviet scientists-pharmacists G.K. Momota and M.M. Molodozhnikov, who showed that cinchon in our country can be grown in the form of a two-year culture, however, the content of alkaloids in such raw materials will be small (about 2%) [2].

However, the quinine story does not end there. Along with work on increasing the efficiency of reproduction of cinchona, research on the synthesis of quinine was actively carried out in the scientific world. Only 34 years after the discovery in 1854, A. Strecker obtained the molecular formula of quinine, and at the end of the nineteenth century. J. Skraup and W. Koenigs described its chemical formula, but it was not possible to synthesize quinine. In April 1944, Robert Woodworth and William von Eggers Doring of Harvard announced the complete synthesis of quinine from xinotoxin, having obtained 30 mg of quinine in their experiments. The discovery of Woodworth and Dorring did not find practical application, since synthesized quinine was very expensive. In addition, doubts arose about the very fact of this discovery, since the synthesis of quinine could not be reproduced for a long time.

Soviet scientists followed the path of creating synthetic antimalarial drugs. The first such drug, plasmokhin, was obtained in our country in 1925, and at present the arsenal of antimalarial drugs is very large. Preparations have been created that act on different types of malaria pathogen at different stages of its development. Quinine itself, which was the main agent in the fight against malaria in the past, to this day "remains in the ranks", but has limited use. Quinine is included in the WHO list of essential medicines, updated in 2013.

An in-depth study of the chemical composition of the cinchona tree bark showed the presence of a number of quinoline derivative alkaloids, the main of which are quinine and its stereoisomer quinidine, as well as their derivatives: cinchonidine and cinchonine. Quinine salts are used as an antiprotozoal agent that acts on all types of malaria plasmodia. Quinidine sulfate is used as an antiarrhythmic agent for tachycardia, atrial fibrillation. Bark tincture and decoction - both stimulating appetite and improving digestion. Cinchona bark is also used in homeopathy.

Quinine has another interesting use. In the 19th century, the number of malaria cases in Europe declined markedly, but the demand for quinine did not diminish. On the contrary, with the expansion of colonial expansion in Asia and Africa, more and more of it was required. The colonies of Holland, France, Spain, Portugal, Germany and Belgium were located in malarial areas, and quinine was needed to prevent malaria. In the British colonies in India, Malaysia, Africa, the Caribbean, malaria was endemic. For the purpose of prevention, the British were forced to take a solution of quinine, and gin was added to mask its bitter taste.

The British habit eventually evolved into a traditional evening gin and tonic. Quinine is now also used as an additive in some soft drinks such as Schweppes and other soft drinks labeled "tonic". In the United States, the maximum allowable level for quinine in beverages is 83 parts per million. The International Joint FAO / WHO Expert Committee on Food Additives indicates that lemonade can contain up to 100 mg / l^{-1} quinine without health risks. However, some individuals may experience a hypersensitivity reaction [8].

The properties of cinchona bark to stimulate appetite and increase the secretion of the glands of the gastrointestinal tract are widely used in the manufacture of aperitifs. Quinine is found in the famous French wine beater Dubonnet, cinchona tinctures Byrrh and Picon. In Russia, until 1917, the highly popular cinchona vodka was produced, the production of which was discontinued during the Soviet era.

CONCLUSION

In the 21st century, the search for other plant sources of quinine, besides the cinchona tree, continues. So in 2005, quinine was isolated from the bark of the Peruvian remidge. Scientists are looking for antimalarial agents of a different, non-alkaloid nature. The result of such studies was the receipt of artemisinin, isolated by Chinese scientists under the guidance of the pharmacologist Tu Yuyu from the qinghao plant - one of the types of wormwood. In 2012, the synthesis of artemisinin was carried out, which significantly expanded the possibilities of its use in medicine for the treatment of parasitic diseases. In 2015, scientists - the developers of this problem, William Compbell, Sotoshi and Tu Yu were awarded the Nobel Prize.

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