“What is all knowledge but recorded experience and a product of history?” said Thomas Carlyle a Victorian Scottish writer. The history of the antimalarial medications only proves him right.

**History of Quinine**

Cinchona tree or Quina (from Indian word “kina” means “bark of the tree”) is a unique natural source of quinine, an important historical remedy against malaria. Peruvian Indians were the first to discover the medicinal properties of the bark of the tree which used to be called a “fever tree”. They stripped, dried and powdered the bark and then mixed the powder with the water obtaining a bitter tasting liquid. They used it to treat fevers for many centuries. Their medicine had curative effect for some infectious diseases like malaria.

Cinchona tree is a genus of about 40 species belonging to the family Rubiaceae. The native region of these trees is in the tropical South America.

The name of the genus Cinchonon quinquina condaminiæ is due to Carolus Linnaeus who named it after Charles Marie de La Condamine in 1742 [1]. This French explorer, a member of the expedition to Peru in 1735, described and published the use of “kina” bark of Peruvian tree to fight malaria. Cinchonon name came from the title of the Countess de Chinchon, wife of the Spanish Viceroy of Peru, who according to legend was the first European cured from malarial attack with the use of the Indian’s medicine.

**Scientific classification**

Order: Gentianales
Family: Rubiaceae
Subfamily: Cinchonoideae
Tribe: Cinchoneae
Genus: Cinchona

The plants were transported to Europe from their native South America in nineteenth century. They have been cultivated since that time in other tropical regions of the world. As European countries continued extensive colonization in Africa, South Asia, and South America, the need for quinine was growing, because of the exposure to malaria occurring in all these regions.

**Quinine – an important historical remedy against malaria**

Spanish Jesuit missionaries in Peru were the first Europeans to appreciate the true value of Cinchona. They disseminated knowledge of its healing power throughout Europe in 17th century. The missionaries were the primary exporters of the Peruvian bark to Europe. The medicine was first used to treat malaria in Rome in 1630s. Information about medicinal cinchona tree started to reach Europe no sooner than in 18th century, however the active components of the bark were still unknown. Alexander von Humboldt and Aimé Bonpland were the first to publish scientific studies about quinine, the most important agent of bark [2].

The economical reasons were the stimulus for starting research aiming at purification of active agents from powdered bark. French researchers J.B. Caventou and P.J. Pel-
letter were the first, who isolated quinine and cinchona in crystalline form in 1820. They refused to have any profit from their discovery. Quinine was the first chemical compound to be successfully used to treat the parasitic infection until World War I. It used to be only effective treatment against malaria. Cinchona trees remained the only source of quinine until 1944, when American chemists R.B. Woodward and W.E. Doering succeeded in synthesizing quinine chemically [3]. Then pharmaceutical laboratories started to produce synthetic Quinine. Again the soldiers were the first beneficiaries of Quinine, this time synthetic.

CINCHONA alkaloids

The bark of the Peruvian Cinchona Tree is the natural source of more than 30 active alkaloids

The main alkaloids are:
- CINOCHONINE and CINOCHONIDINE (stereoisomer with R = vinyl, R’ = hydrogen),
- QUININE and QUINIDINE (stereoisomer with R = vinyl, R’ = methoxy),
- DIHYDROQUINIDINE and DIHYDROQUININE (stereo isomers with R = ethyl, R’ = methoxy).

For medical purposes the most useful are quinine and its stereoisomer quinidine. Quinine ((R)-(6-methoxyquinolin-4-yl)((2S, 4S, 8R)-8-vinylquinuclidin-2-yl) methanol) is a natural white crystalline alkaloid that contains two major fused-ring systems: the aromatic quinoline and the bicyclic quinuclidine. Quinine is very sensitive to ultraviolet light (UV) and will fluoresce in direct sunlight, due to its highly conjugated resonance structure.

Quinine has antipyretic, antimalarial, analgesic, muscle relaxant, and anti-inflammatory properties. Quinine was the first chemical compound to be successfully used to treat the parasitic infection, especially malaria [4].

Quinidine unlike the quinine is used mainly for cardiac rhythmic disorders. It is classified as an antiarrhythmic drug (class I).

Malaria

Malaria is still a serious illness causing death worldwide. Each year, this disease kills more than 1 million people, mostly children. The name is derived from the Italian “mal-aria” which means “bad air”.

Malaria is the parasitic (plasmodia) disease common in tropical and subtropical regions of Africa, Asia and both Americas. Currently over 200 species of this genus are recognized; at least 11 species infect humans. Severe disease is mainly caused by Plasmodium falciparum, which is predominant species. Malaria caused by Plasmodium vivax, Plasmodium ovale and Plasmodium malariae is generally a milder, rarely fatal disease. Plasmodium sporozoites from the saliva of biting female mosquito are transmitted to either the blood or the lymphatic system. The majority of sporozites migrate to the liver and invades hepatocytes. The disease results from the multiplication of malaria parasites within human red blood cells. Typical symptoms include fever, shivers and headache, haemolysis and in severe cases the disease leads to coma and eventually to death.

Mechanism of action of antimalarial drugs

The mechanism of action of antimalarial drugs is still unclear. The most widely accepted hypothesis is that Quinine and other antimalarials act by interfering with the growth and reproduction of the Plasmodium in human red blood cells. Action of the malarial parasite degrades hemoglobin to acquire essential amino acids, which the parasite requires to construct its own protein and for the process of energy metabolism. During this process, the parasite produces a toxic and soluble molecule heme. The parasite biocrystallizes heme (or FP) into insoluble and non-toxic hematin.

The drugs enter red blood cells, inhabiting a parasite cell, and digestive vacuole by simple diffusion. Antimalarials inhibit the hemozoin biocrystallization process by raising the internal pH in the digestive vacuoles of parasites. The aggregation of cytotoxic heme results in cell lysis and ultimately parasite cell autodigestion [5]. Other potential mechanism is interfering with the biosynthesis of parasitic nucleic acids.

Quinine is highly active against the erythrocytic form of Plasmodium, however it fails to make the malarial parasites in other cells disappear. These parasites persist and, after a time, they reinvade the red blood cells and precipitate the relapse. As quinine was not permanently effective and after a time, they reinvade the red blood cells and precipitate the relapse. As quinine was not permanently effective and after a time, they reinvade the red blood cells and precipitate the relapse. As quinine was not permanently effective and after a time, they reinvade the red blood cells and precipitate the relapse. As quinine was not permanently effective intensive research was conduct to develop new antimalarial drugs [6].

Many drugs were synthesized to protect military troops from malaria particularly during and after the Second World War. Some of these drugs (such as chloroquine, mefloquine and chloroguanide) are more effective than quinine in suppressing the growth of the blood forms of the malarial parasite. Others (such as primaquine and pyrimethamine) act upon both the blood and tissue phases of the parasite, enabling a complete cure and preventing a relapse.

Currently there are many medications against malaria, both for prevention and treatment like atovaquone, proguanil, artemether, lumefantrine, dihydroartemisinin, piperaquine, and antibiotics like doxycycline, clindamycin. Nevertheless quinine is still very effective in the treatment of acute cases of severe malaria, especially against Plasmodium falciparum.

Antimalarial drugs and autoimmune diseases

The antimalarial drugs like as the anti-inflammatory drugs have also the propriety to decrease pain, swelling,
and prevent joint damage and disability. Therefore these medications could also be useful to treat some chronic, inflammatory disease with rheumatic disorders [7, 8]. Among them, autoimmune diseases, like lupus erythematosus (SLE) as well as rheumatoid arthritis (RA) which are characterized by a wide variety of symptoms, although known mainly for arthritis [9].

Doctor T. Payen of St Thomas’ Hospital in London was the first to recognize beneficial effect of quinine in the treatment of discoid lupus in 1894. He reported benefits of therapy both in case of fever and joint pain in lupus as well as the skin problems. Subsequently, quinine and the other antimalarial drugs have been prescribed for SLE, RA and Sjögren’s syndrome [10-12]. They are considered to be disease-modifying-anti-rheumatic drugs (DMARDs).

Autoimmune diseases show tendency to make the immune system go into overdrive. Mechanism of action DMARDs is related to their special proprieties: immunologic activity, anti-inflammatory effects, UV light absorption, hormonal actions, antyproliferative activities, antimicrobial effects, and inhibition of platelet’s aggregation and adhesion [13].

**Antimalarials – immunotropic action**

Antimalarial drugs block antigen processing by raising the pH in the cell, thus interfering with intracellular enzyme activity. This immunologic action decreases production of immune mediators: cytokines like interleukin I, II and tumor necrosis factor. Antimalarials inhibit natural killer-activity and intracellular toll-like receptors (TLRs) particularly TLR9. Toll-like receptor 9, which recognizes DNA-containing immune complexes, leads to the production of interferon and causes the dendritic cells to mature and present antigen to T cells. Antimalarials, by decreasing TLR signaling, reduce the activation of dendritic cells thus mitigating the inflammatory process. They decrease auto-antibody production, inhibit the proliferative response of lymphocytes and have a direct effect on DNA [14-16]. In these ways antimalarials have the potential to put the disease into remission [17-19].

Antimalarials inhibit platelet aggregation and adhesion. This important anti-clotting effect is very useful in treating patients with the antiphospholipid syndrome. It is also known that these medications protect against damaging effects of ultraviolet light and can improve skin lesion.

The immunologic action of antimalarial drugs may have an immunosuppressive effect on the response to vaccination. It should be taken into consideration in case of vaccinating patients with autoimmune diseases treated by antimalarials.

The drugs belonging to the family of antimalarials are rather similar but nevertheless, have different side effects. The most serious unwanted side effect is irreversible retinal damage. Retinopathy has been reported to be dose and drug related [20]. Hydroxychloroquine [2-[(4-[(7-chloro-4-quinonyl) amino] pentyl) ethyamino] ethanol sulfate] is considered to be less toxic, less indigestible and having fewer side effects than others [21, 22]. The drug was synthesized in 1946 and approved by FDA in 1955.

Hydroxychloroquine is classified as an anti-malarial medication. It is commonly used in treating lupus erythematosus, rheumatoid arthritis and Sjögren’s syndrome [23].

Unfortunately most strains of *Falciparum malaria* are now resistant to this drug so patients taking hydroxychloroquine for autoimmune diseases are not any longer protected against malaria.

**Conclusions**

The above story is a good example of the progress of our knowledge based on evidence and experience. Starting from the moment of discovery of curative effects of barks of Kina Tree by Indians, for centuries of observations and research finally achieving modern phytoneering.

However, despite enormous progress in our understanding of the disease, and implementation of new drugs, malaria remains one of the most common cause of serious illness and death in the world. Although many effective antimalarials have been introduced, quinine is still being used to treat the disease in certain critical situations. None of the prophylactic treatment proved to be fully effective against malaria infection. Drug resistance also poses a serious clinical problem.

The problem of finding an effective and safe treatment of autoimmune diseases has not been solved yet, either. The currently used drugs are often as toxic and harmful as the disease itself.

Thus, there is a great need to continue research for better understanding of inflammatory and immune processes.

New approaches to taking advantage of available chemotherapy or immune-modifying technology in successful of malaria and autoimmune-diseases are badly needed.

**References**