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THE DEVELOPMENTAL PATH OF QUININE: WHAT CAN WE LEARN FROM HISTORY?

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Almost 200 years have passed since the pure substance was first isolated, but scientists still face similar challenges. Quinine—the first chemotherapeutic agent in the treatment of malaria—is one of the good examples from history that testifies to the challenges in drug development.

The aim of the paper was to present the history of the discovery and synthesis of quinine and its importance in medicine.

Descriptive research was conducted using secondary data sources during September and October 2022.

Quinine is one of the first active substance whose effectiveness has been proven in clinical research. Its widespread consumption soon led to a shortage of quinine, and new sources of this valuable active substance had to be provided. The challenges of plantation cultivation were solved by developing botany and its chemical synthesis through organic chemistry. By researching quinine, numerous pharmacologically active substances such as caffeine and methylene blue were found, which would start a revolution in the chemical industry and the industry of organic synthesis. With the development of resistance to antimalarials, quinine experienced its heyday again because it proved to be effective even in resistant strains.

Quinine represents a significant historical discovery that influenced the development of many scientific disciplines, primarily pharmacy, medicine, and organic chemistry. The history of quinine provides us with an important historical lesson that we need to be aware of in today's time when the pharmacy is facing the significant challengesof developing new drugs. *Acta Medica Medianae 2023;62(2): 61-70.*

Key words: *quinine, history of pharmacy, drug development, antimalarial drugs*

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Introduction

The era of isolating pure active substances from plants started more than 200 years ago. More precisely, it was started in 1804 by a 23-year-old apothecary's apprentice Friedrich Willhelm Sertürner (1783–1841). He isolated the first pharmacologically active substance from opium obtained by cutting seed pods of the poppy, *Papaver somniferum* calling it morphine after Morpheus, the Greek god of dreams (1–4). Such and similar discoveries resulted in precise dosing and, therefore, in achieving greater efficiency in treatment, representing a type of revolution in medicine. With pure active substances, clinical experiments that could investigate the effectiveness of treatment on a quantitative basis are rapidly developing. Life expectancy in most of the world has increased from about 40 years earlier in the 20th century to more than 77 years today (5).

Some of the most significant isolations of pharmacologically active substances are shown in Table 1, created according to the paper of the author Prarojčić D. et al. (6). The discovery of synthetic drugs followed a little later, at the beginning of the 20th century. Some of the major therapeutic discoveries were the synthesis of barbitone (Veronal)—the first "true" hypnotic compound in 1903 (7) and arsphenamine (Salvarsan)—the first effective treatment for syphilis in 1910 (8); and the isolation of thyroxine in 1919 and insulin in 1922. One of the main discoveries was in 1928 when Alexander Fleming observed the antibacterial action of the mould *Penicillium notatum* (9).

Table 1. The most significant isolations of pharmacologically active substances

A year of isolation	The name of the active substance
1804	Morphine
1817	Nicotine
1818	Strychnine
1819	Brucine
1820	Colchicine
1833	Atropine Aconitine
1848	Papaverine
1890	Scopolamine

In the past, scientists generally came to the development of new drugs in two ways: accidental discoveries where the creativity, intuition, and meticulousness of researchers were of crucial importance (10, 11), while the other was the observation of specific side effects of the drug and their translation into positive therapeutic effects (3). Nowadays, when the pharmaceutical market is full of competition, there are unrealistically high expectations for discovering and producing "blockbuster drugs" (12). Most of the current difficulties in the pharmaceutical industry can be divided into two categories: the prevailing paradigm for drug discovery in large pharmaceutical industries and the limitations in identifying new compounds with the desired activity (13). Many large pharmaceutical companies have reduced their interest in using natural products in drug discovery screening, focusing on modern techniques (14, 15). However, natural products are still the only abundant sources of potential candidates ("lead" compounds) for developing new drugs (16). With new improvements in spectroscopy, analytical technologies and high-throughput screening, natural products can experience a renaissance in discovering new drugs (17).

The history of drug discovery and synthesis is full of stories of luck and perseverance. One such historical story is the quinine story, which actually begins with the history of plant usage. Quinine bark has long been used to treat malaria, an infectious disease that has caused perhaps even the most significant mortality in human history (18–20). The Peruvian Indians first discovered the effects of quinine bark on malarial fever, and after the colonization of Peru, the quinine bark reached Europe. Quinine bark soon received many names such as “cinchona bark”, "Peruvian bark", "Jesuit's powder", "cardinal's bark", "countess's powder" or "royal powder" (21).

Quinine bark extract was the first—and, for a long time, the only—effective medicine against fever, especially intermittent fever. The first notes of the use of quinine bark date back to the 17th century, after which the medical literature contains countless reports on the treatment of malaria using quinine bark and about a thousand specific studies on the subject (22). The use of quinine bark in England was founded by the London apothecary Sir Robert Talbor. He was making a secret, very successful preparation based on quinine bark. However, the secret was revealed in his posthumous book: *The English Remedy: or, Talbor's Wonderful Secret for Cureing of Agues and Feavers*. He combined Peruvian bark with rose leaves, lemon juice and wine (23).

Claims of its effectiveness often varied depending on the nationality of the practitioner as much as the quality (bitterness) of the bark (24). The high variability of the antimalarial effect of the quinine bark preparation was one of the main difficulties in using the bark. That variability came mainly from the type of Cinchona tree, the place where the bark was obtained, and several other variables that affected the active principle content of the bark. Franceso Torti was the first to conduct systematic studies on the effects of quinine bark on various types of fever in 1712 (21, 23).

Quinine bark was also used in the prevention of malaria, which is confirmed by the words of William Buchan, who, in 1781, wrote: "Take an ounce of the best Jesuits' bark, Virginian snake root, and orange peel, of each half an ounce; bruise them all together, and infuse for five or six days in a bottle of brandy, Holland gin, or any good spirit; afterwards pour off the clear liquor, and take a wine-glass of it twice or thrice a day". This may be the first recipe for gin and tonic

water (25). Quinine bark was used to combat malaria in soldiers during the siege of Belgrade in 1717 (26).

In addition to the treatment of malaria, quinine bark was also used in the treatment of ulcers, hemorrhoids, inflammation of the stomach, intermittent neuralgia, hemoptysis. The Pharmacopée universelle describes more than 100 official preparations based on quinine bark powder or bark extracts, which are believed to have special properties against a wide range of diseases, for example typhus or used as a tonic (21).

As a medicine that saved many lives, it had enormous importance and occupied the great attention of scientists of that time. In the era of great discoveries, when many other active substances from plants were discovered and isolated, quinine was also isolated—the active ingredient of the quinine bark. Quinine was isolated in 1820 by two French pharmacists, Pierre Joseph Pelletier and Joseph Caventou, after which quinine replaced the bark as the standard treatment for malaria (20, 27). By 1826, these chemists were producing over 3,500 kg of quinine sulfate each year, which can be considered the beginning of the modern pharmaceutical industry (28). Unlike other scientists, they made their process freely available, that is, they did not patent it (29). With the isolation of quinine, the first chemotherapeutic agent in the modern sense of the word was born (19, 21).

Therefore, this paper aims to present the history of the discovery and synthesis of the first drug used in malaria therapy and its importance for the development of pharmacy and medicine, to serve as a lesson about perseverance, effort, and hard work.

Methodology

We have conducted descriptive research in which mostly secondary data sources were used. The PubMed database and relevant websites were searched during September and October 2022. The following keywords were used during the search: "history", "cinchona", "quinine", "antimalarial drugs", and "malaria." After that, a selection of relevant works and websites was made. The next step was reading and analyzing the selected works. The final step was data synthesis.

Results and Discussion

Quinine—isolated active substance

With the pure quinine substance, the dosage becomes precise. It can be adjusted to the individual needs of patients, as a result of which the effectiveness of malaria treatment has increased many times. Since Pierre and Joseph were pharmacists with less experience, they left to more experienced doctors to prove the effectiveness of the newly isolated natural product. They soon confirmed its effectiveness, established its specificity in the therapy of occasional (malarial) fevers, and by the end of 1821, gave instructions for its use in *Formulaire pour la préparation et L'emploi de plusieurs nouveaux médicaments* (30, 31). First, its safety was tested on dogs, and when it was defined as safe for use in therapeutic doses, it was tested on hospital patients. The results were as expected—quinine achieved remarkable efficacy, and numerous medical observations and case reports from around the world soon pointed to its specificity for "malarial" fevers. However, isolated quinine had a much higher price than the quinine bark, so the question arose: is it profitable to use quinine instead of cheaper crude extracts of the bark? Soon scientists come to a very simple conclusion: quinine or its salts should be used instead of bark extract to treat intermittent fevers (21).

The dose of quinine that was used for therapeutic purposes was adjusted to the dose of quinine bark that was previously used, which led to significant variability in dosage. Most doctors gave their patients 3–5 grains (approximately 0.2–0.3 grams) of quinine no more than 2 times a day, while some administered 5 grains every 6 hours. Italian physicians have reported using up to 25 grains daily to treat severe and relapsing intermittent fevers. Despite these variations and uncertainties, a consensus has been reached on treatment: apply 5 to 15 grains of quinine daily, divided into several doses. Discussions about the method of application and dosage of quinine continue to this day. Warrington Yorke best described these methods. He stated that “The use of quinine has been known for 300 or 400 years, yet no one is even now able to state how the quinine should be taken, in what manner, and in what doses” (21, 32, 33).

Following the hypothesis that quinine is found in the coffee tree (because it belongs to the same family as quinine), numerous studies followed, which resulted in the isolation of caffeine in 1821. Soon other alkaloids were isolated from the bark of the quinine tree: firstly quinidine, cinchonine, and cinchonidine, and an additional 25 alkaloids related to quinine were isolated by 1884, and 6 more between 1884 and 1941. Pasteur, a versatile French scientist, produced several "toxins" (cinchotoxin and quinotoxin—known initially as quinicine) from quinine, which would prove crucial 50 years later during the first attempt to synthesize quinine, and their role is still prominent in today's science (30).

With the colonization of malarial parts of the world, the demand for quinine became even more remarkable, and the supply of herbal drugs from South America became insufficient (23, 34). In the mid-19th century, bark and pure quinine were always in short supply as they were the only known effective treatment against malaria. This initiated ideas of plantation, cultivation, and

synthesis of quinine, as the only possible alternatives to ensure a continuous and abundant supply of quinine (23, 30).

Cultivation of cinchona tree

Although the plantation cultivation of cinchona tree looks very simple at first glance, at the time, it was a big challenge. In the beginning, numerous expeditions were organized in search of trees, seedlings, and seeds of quinine, but the lack of botanical knowledge made the cultivation unsuccessful (37). At that time, quinine was cultivated in Ecuador, Peru and Bolivia, and the export of quinine seeds was strictly prohibited. England took the lead in these expeditions, and the entrepreneur Charles Ledger, in 1865, finally got hold of several kilograms of high-producing quinine plant seeds and began its cultivation. The seedlings were grown at Kew Gardens from where they were to be distributed to where they would be planted (21, 25).

The first cinchona plantation established outside the American continent was in Ceylon and India, and the quantity of the drug was sufficient to meet the needs of the English colonial army (30, 35). However, the Dutch soon set up a plantation in Java thanks to Charles, who sells them cheap seeds, because the English government was not interested in buying them (25, 30, 36). Due to the favorable climatic conditions, these plantations became the primary sources of quinine bark and the Netherlands took control of the world trade in quinine, with more than two-thirds of the world's share, until the Second World War, when Japanese control of Java forced the Allies to look for alternative supplies and synthetic substitutes for quinine. Until 1913, quinine bark was characterized by low prices, but that year the "Quinine Agreement" came into force, which established a specific, higher price for the bark, thus creating the first pharmaceutical cartel in the world (37, 38). Figure 1 taken from a 2013 paper by Goss A. shows workers on a cinchona plantation in Java (39).

During the period of British colonization of India and other tropical countries, in the early 19th century, medicinal quinine was recommended to British officials and soldiers as a prophylactic against malaria, where it was mixed with soda and sugar to mask its bitter taste, forming tonic water (40).

Figure 1. Workers on the Cinchona plantation Ramawatie, West Java. Collection Tropenmuseum, Amsterdam, coll. nr. 10012774. Taken from reference 39

Synthesis of quinine

However, this second strategy proved to be a much more demanding task. It will take almost a century to be realized. Nevertheless, the synthesis of quinine would bring about a scientific revolution and play an important historical role in organic and pharmaceutical chemistry (30).

The first to speak of the challenge of its synthesis was August Wilhelm von Hofmann, then director of the Royal College of Chemistry in London, who in 1849, declared his intention to synthesize the lucrative quinine to demonstrate the ability of organic chemistry to solve social needs. Shortly after that announcement, the race for synthetic quinine heated up. The French Pharmaceutical Association invites chemists by offering a prize of 4,000 francs to one who first synthesizes quinine. No one claimed this award (30).

Chemical synthesis was in its infancy at the time. Scientific research in this area has often been done by trial and error based on intuition. Moreover, there were no related concepts for the structure of compounds (these ideas appeared a decade later with the development of structural theory). The molecular formula of quinine postulated by Hoffmann ($C_{20}H_{22}N_2O_2$) had two hydrogen atoms less than the correct formula ($C_{20}H_{24}N_2O_2$) established by Adolf Strecker in 1854. This knowledge prompted the beginning of the experimental phase of Hoffmann's project. Soon, however, economic support begins to wane due to the impatience of wealthy sponsors who

worry about the lack of results from their investments and begin vehemently debating the true virtues of applied organic chemistry and its ability to produce something worthwhile (41).

During the Easter holidays of 1856, knowing the exact molecular formula of quinine and following the ideas of his mentor Hoffmann, eighteen-year-old William Henry Perkin decided to "reproduce" quinine (42). However, the experiments were mostly unsuccessful. In one of his many experiments, he accidentally discovered the first synthetic aniline purple dye called "mauve", which launched the synthetic dye industry and the birth of the modern chemical and organic synthesis industries (43–45). Perkin developed processes for the mass production of paint and, in 1857, with the financial support of his father, opened a factory near London to commercialize his discovery. It was the world's first large organic chemical factory, the beginning of the aniline dye industry, which itself was the initial driving force in the global chemical industry (19, 30, 32).

Paul Ehrlich soon discovered that methylene blue was particularly effective in staining malaria parasites. Under this assumption, the dye had a toxic effect on parasites. Together with Guttmann, he used this drug in 1891 to treat malaria. Methylene blue therapy proved successful and became the first synthetic drug ever used in therapy (46, 47). Methylene blue also contributed to the development of many antipsychotics and antidepressants that were discovered after substitution of side groups on the methylene blue scaffold (48).

In the next 50 years, there were no serious attempts at synthesis. However, structural theories were developed in that period, and organic chemists realized that the structure of quinine is more complex than previously thought and that elucidating the structure was the first cork in a rational approach to synthesis. It was a great challenge for the chemists of that era and required the application and combination of all previous knowledge in chemistry. A breakthrough occurred in 1908 when Paul Rabe theorized the correct chemical structure of quinine, but some stereochemical questions remained unresolved, and research continued (30, 49).

World turmoil during the First World War made it impossible for Germany to supply quinine from Java. As a result, German soldiers who fought in southern Europe suffered greatly from malaria. In order to prevent this event from happening again, German pharmaceutical chemists were engaged in the 1920s to find a synthetic alternative to quinine, which they succeeded in doing. The first effective aminoquinoline drug in the treatment of malaria was pamaquine, synthesized in 1926 (50). By 1932, they had synthesized quinacrine, also known as mepacrine (Atabrine®), a simplified version of quinine (51). This drug became the main drug used in the treatment of malaria during the Allied war operations in the Pacific, despite the fact that the skin of its users became yellow (52). Its use was enforced by giving it at mealtimes and warnings about the danger of not taking it. One sign posted at a hospital in Papua New Guinea had two human skulls mounted on a bulletin board that read "These men did not take their Atabrine" (40).

While the search for the structure was still going on, Rabe and Kindler, in 1918, took the first big step towards synthesizing quinine since Perkin's famous "failure" by presenting a synthetic sequence for obtaining quinine and quinidine from quinotoxin. After countless experiments, assembling scientific results like a mosaic, in 1931, Paul Rabe determined the final stereochemical structure of quinine, thereby opening the door wide to its synthesis (30).

The Second World War brought similar problems. America was left without quinine due to the Japanese conquest of the Javanese territory. Therefore, the mepacrine trade between the USA and Germany stopped. American soldiers who fought in the Pacific ran out of malaria medicine and fell victim to it (53). Although they soon developed their synthesis of mepacrine, Americans fell under the influence of Japanese propaganda called "Tokyo Rose," in which the Japanese spread the lie that mepacrine causes sterility. Many Americans stopped using it and fell victim to malaria. This led to the development of new antimalarials such as santoquine and chloroquine, but also to the investment of significant additional efforts for the total synthesis of quinine. Chloroquine was first synthesized in 1934 by H. Andersag, an industrial chemist of the Bayer Company, under the name Resochin®. After synthesis, its effects on birds infected with malaria were tested, where it was determined that it was as effective as Atabrine, but more toxic. This led Bayer to abandon the development of this drug. However, the development of chloroquine in the USA began in 1943, and it was evaluated on dogs and monkeys, with the latter study showing that it was four times less toxic than sontaquin. After that, in 1946 it was chosen as the drug of choice for the treatment of malaria (23, 54). Santoquin was synthesized by Bayer industrial chemists in 1936 as an attempt to develop a less toxic analogue of chloroquine (55). In 1946, primaquine was synthesized in America, replacing the side chain terminal NEt2 group with an NH2 group, in order to reduce the toxicity of pamaquine (56).

Finally, in 1944, Robert B. Woodward and William von Eggers Doering at Harvard University reported the first total synthesis of quinine—the most famous cinchona alkaloid claimed to be "the drug that has alleviated human suffering more than any other in history". In Figure 2, taken from a paper by Ball published in 2008, we can see Robert Woodward and William Doering. That was the end of the almost 100-year era of man's attempt to master this unique product of nature.

This discovery led to Robert and William being hailed as heroes (32). However, there was

one problem. They succeeded in synthesizing hinotoxin, and Rabe and Kindler took over the further procedure of its translation into quinine, but they failed to repeat it. That is why research into the synthesis of quinine continues. In 1970, Milan Uskoković and co-workers discovered the first real total synthesis of quinine. Another great success in this field was achieved in 2001 when Gilbert Stork published the first total stereoselective synthesis of quinine (57, 58).

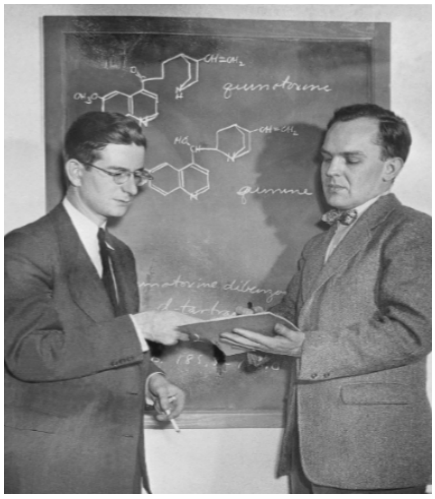

Figure 2. Robert Woodward (left) and William Doering (right). Figure taken from reference (32)

Quinine therapy

Quinine is a short-acting drug with an extremely bitter taste. In therapeutic doses, it often causes a series of unpleasant symptoms known as cinchonism that include tinnitus, dizziness, headache, dysphoria, nausea and vomiting. Nevertheless, the availability of quinine as a pure active substance allowed it to be widely used in the prophylaxis of malaria, especially among soldiers. However, even in frequent repeated doses that can cause cinchonism, quinine does not actually prevent infection (59). That is why the soldiers avoided using it. In Figure 3, taken from the work of the author Eiden published in 1998, we see propaganda material urging soldiers to use quinine: Soldier, take your quinine daily (60).

Figure 3. Propaganda material urging soldiers to use quinine. (E. Chast Collection, Paris. From the exhibition catalogue "De l'élixir au génie génétique—deux siècles de sciences pharmaceutiques hospitalières", Paris 1995). Figure taken from reference (60)

The famous "Koch's method" of quinine application states that the widespread use of quinine would not only cure individuals but, if used by all infected persons, would break the cycle of re-infection and could lead to the elimination of malaria. This method was encouraged by the Governments of certain countries, which led to a new expansion of the use of quinine (39).

Quinine was one of the first drugs produced by the world's pharmaceutical industry. Factories

processed quinine bark, extracting the alkaloid quinine, converting it into quinine sulfate, which were suitable for medical use. The doses of quinine that were established immediately after the discovery of quinine have not been changed for years. Unlike the dose, the length of therapy varied from a few days to a few months. Before the acute phase of malaria, 1 g of quinine was administered, followed by smaller daily doses (0.25–0.4 g) over a longer period of time. However, the discussions about dozing of quinine did not stop. This later led to changes in the treatment protocol. Very high doses of quinine have been used in fevers that did not respond to lower doses. However, those high doses led to very toxic effects (21, 39).

Until the availability of effective synthetic antimalarial drugs in the late 1940s, quinine was the only reliable antimalarial drug. Because of its side effects, its use as a first-line treatment is limited, but it is still valuable as an adjunct to other treatments and can save lives. After the development of other antimalarial drugs, quinine was briefly neglected. However, with the development of resistance to antimalarials, quinine experienced its heyday again because it proved to be effective even in resistant strains (61). As of 2006, WHO no longer recommends quinine as a first-line drug for malaria.The 2010 WHO guidelines recommend a combination of quinine and doxycycline, tetracycline, or clindamycin as the second-line treatment for uncomplicated malaria, and a combination of quinine and clindamycin for the treatment of malaria in the first trimester of pregnancy (18).

Quinine continues to play a significant role in the management of malaria in sub-Saharan Africa and other malaria endemic areas. For example, in Uganda, quinine is prescribed for up to 90% of children <5 years of age with uncomplicated malaria (62).

By 2009, 31 African countries recommended quinine as a second-line treatment for uncomplicated malaria, 38 as a first-line treatment for severe malaria, and 32 for the treatment of malaria in the first trimester of pregnancy (63). There is no doubt that quinine will continue to play an essential role in human history soon (18).

Conclusion

Quinine represents a significant historical discovery that influenced the development of many scientific disciplines, primarily pharmacy, medicine, and organic chemistry. In addition, quinine, as the first effective antimalarial drug, saved many lives and significantly contributed to the public health of that era. However, the challenges faced by scientists were significant. Although they had well-established hypotheses, in order to prove them, particular prerequisites, such as advances in analytical techniques and chemical theories, had to be developed. Scientists followed their intuition even when everything pointed to them being wrong. However, patience, meticulousness, and persistence made them prove their hypotheses and make significant discoveries. From this, we should learn an important historical lesson by emulating the scientists of that time because today's scientists are also facing similar challenges.

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Declaration of competing interest

None declared.

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RAZVOJNI PUT HININA – ŠTA MOŽEMO NAUČITI IZ ISTORIJE

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Prošlo je skoro više od 200 godina od prvog izolovanja čiste supstance, ali se naučnici i dalje suočavaju sa sličnim izazovima. Hinin, prvi hemoterapeutik u terapiji malarije, jedan je od dobrih primera iz istorije koji svedoči o izazovima u razvoju lekova.

Cilj ovog rada bilo je prikazivanje istorije otkrića i sinteze hinina i njegovog značaja za razvoj farmacije i medicine.

Sprovedeno je deskriptivno istraživanje korišćenjem sekundarnih izvora podataka tokom septembra i oktobra 2022. godine.

Hinin je jedan od prvih lekova čija je efikasnost dokazana u kliničkim istraživanjima. Široka potrošnja ubrzo je dovela do deficita hinina, te su morali da se obezbede novi izvori ove dragocene aktivne supstance. Izazove plantažnog gajenja rešio je razvoj botanike, a izazove hemijske sinteze razvoj organske hemije. Prilikom istraživanja hinina pronađene su brojne farmakološki aktivne supstance, poput kofeina i metilensko plavog, što je pokrenulo revoluciju hemijske industrije i industrije organske sinteze. Sa razvojem rezistencije na antimalarike, hinin ponovo doživljava svoj procvat, jer se pokazao efikasnim i kod rezistentnih sojeva.

Hinin predstavlja značajno istorijsko otkriće, koje je uticalo na razvoj mnogih naučnih disciplina – farmacije, medicine i organske hemije, pre svega. Istorija hinina pruža značajnu istorijsku lekciju, koje treba da budemo svesni u današnje vreme, kada se farmacija suočava sa velikim izazovima razvoja novih lekova. *Acta Medica Medianae 2023;62(2):61-70.*

Ključne reči: *hinin, istorija farmacije, razvoj leka, antimalarici*