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ABSTRACTS OF RECENT CHINESE PUBLICATIONS ON MALARIA<sup>1</sup>

# Abstracts of Chinese  
- Bibliography of Malaria  
- Review - China

21. Chen, P. H. et al. Preliminary study on the in vitro cultivation of ookinetes of rodent malarial parasites. Chinese Journal of Zoology, 1981 (1) : 1 (In Chinese)

The in vitro cultivation of sporogonic forms of rodent Plasmodium will be helpful to its biological study and to the in vitro cultivation of human malarial parasites. In this study on the in vitro cultivation of Plasmodium yoelii yoelii ookinetes carried out in 1977 and 1978, seven kinds of medium were used in the experiments. Blood, positive for gametocytes, was taken from the tails or orbits of infected mice and was mixed with different media in various proportions. Culture bottles were incubated at 19-25°C. Mature ookinetes were found in gametocyte-positive mouse blood only in four kinds of medium: (i) mosquito extract with mouse blood and heparin in the proportion of 3:3:2; (ii) BME synthetic medium with mouse blood (1:1-3); (iii) Locke's solution with mouse blood (2:1); and (iv) heparin with mouse blood (2:3). Better results were obtained with the first two media. The morphology of ookinetes was similar to that of ookinetes which have developed in the hemocoel of mosquitos. The following factors may influence the formation of P. y. yoelii ookinetes during cultivation:

- (a) temperature: the optimum temperature range is 19-25°C, higher temperature being inhibitory to the formation of microgametes.
- (b) number and viability of gametocytes: in general, the number of gametocytes is in direct proportion to the number of ookinetes formed. The suitable time to take gametocytes containing rodent blood is 3-5 days after inoculation and within 1-5 generations of subinoculation.
- (c) the phagocytosis of white blood cells: the number of ookinetes formed is in inverse proportion to the number of white blood cells, a phenomenon which may be due to the phagocytosis of white blood cells.

22. Li, Z. Y. Plasmodium knowlesi infection in man (one case report). National Medical Journal of China, 1980, 60 (11): 661 (In Chinese)

A 38 years old male patient came to see a doctor with the complaint of intermittent rigour and high fever, beginning every midday since three days and accompanied by headache, thirst and anorexia. He had worked in a laboratory where monkeys and Anopheles balabacensis infected with Plasmodium knowlesi had been kept for three years since 1976. Examination showed paleness and hyperpyrexia, his body temperature reaching 40.5°C. His white blood cell count was 5400 mm<sup>3</sup> with 84% polymorphonuclear. No abnormal finding was noticed on fluoroscopy of the chest. P. knowlesi was identified on blood film and the parasite count was 3934 mm<sup>3</sup>.

<sup>1</sup> The WHO/MAL series has been chosen as a vehicle for issuing abstracts or translations in English of papers on malaria published in the Chinese medical and scientific press as most of this material is not readily available to interested readers outside China. The numbering of the abstracts in this document is consecutive to that of the abstracts given in the previous WHO/MAL/81.933.

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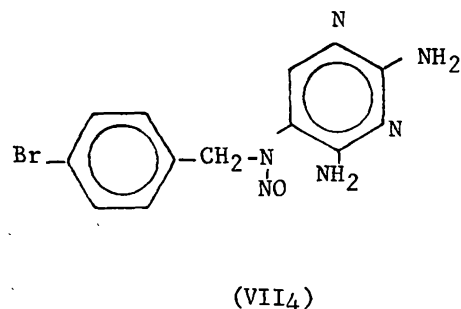
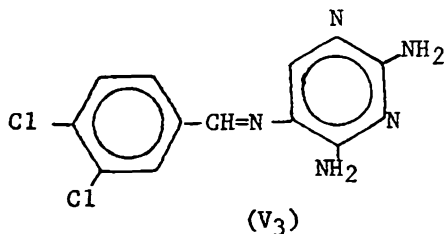
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One ml of the patient's blood was collected and given intravenously to a rhesus monkey. The monkey died showing a severe parasitaemia of 1246 parasites per 200 white blood cells. The patient was cured by Qinghaosu of which a total dose of 800 mg was given over three consecutive days in association with 120 mg of primaquine. At 24 hours after chemotherapy, the patient's temperature had returned to normal and the parasites had disappeared from his blood.

23. Zhang, X. P. et al. Studies on antimalarial drugs. I. Synthesis and antimalarial activity of some derivatives of 2,4-diamino-5-substituted aminopyrimidines and 2,4-diamino-6-methyl-5-substituted aminopyrimidines. Acta Pharmaceutica Sinica, 1980, 15 (12): 711 (In Chinese, with English abstract)

The synthesis of a series of 2,4-diamino-5-substituted aminopyrimidines and 2,4-diamino-5-substituted aminopyrimidines was carried out by condensation of 2,4,5-triaminopyrimidines or 2,4,5-triamino-6-methylpyrimidines with substituted benzaldehydes to form the corresponding Schiff base compound V followed by hydrogenation with sodium borohydride to give 2,4-diamino-(6-hydrogen or methyl)-5-(substituted benzylamino) pyrimidines (VI). Compounds VI then underwent nitrosation by sodium nitrite or formylation by formic acid to obtain 2,4-diamino-(6-hydrogen or methyl)-5-[(substituted benzyl)-N-nitrosoamino] pyrimidines (VII) or 2,4-diamino-(6-hydrogen or methyl)-5-[(substituted benzyl)-N-carboxylamino]-pyrimidines (VIII) respectively.

By using the Plasmodium yoelii-Anopheles stephensi system, these compounds were screened for their prophylactic activity. Two of them, 2,4-diamino-5-(3,4'-dichlorobenzylidene amino) pyrimidine (V<sub>3</sub>) and 2,4-diamino-5-[(4'-bromobenzyl)-N-nitrosoamino] pyrimidine (VII<sub>4</sub>), when administered orally at a dose of 10 mg/kg body weight for 3 consecutive days were more effective than the others, as shown by the protection from infection of the experimental mice.



24. Chen, L. et al. Studies on antimalarial drugs. II. The causal prophylactic activity of antimalarials in animal model. Part I. Plasmodium yoelii-Anopheles stephensi system. Acta Pharmaceutica Sinica, 1981, 16 (4): 260 (In Chinese, with English abstract)

For the purpose of screening new causal prophylactic antimalarials, the Plasmodium-yeelii-Anopheles stephensi system was used. It was demonstrated that the infection rates of Anopheles and mice were  $33 \pm 4.05\%$  and  $94 \pm 0.01\%$  respectively. Mice were fairly susceptible to parasite infection as shown by the more or less constant and high infection rate in the control groups of different batches of experiments. Based on the results of a number of experiments, a routine procedure is suggested for primary screening of drugs as follows. Mice are intraperitoneally injected with the sporozoites of P. yoelii at a rate of one infective mosquito per mouse. Immediately after infection, the drug to be tested is administered once, followed by two other administrations in the next two days. Blood examination for parasites is made on the seventh and fourteenth day after drug administration. In the case of negative

findings, blood pooled from about half of the negative mice is inoculated into normal mice, and the mice in the other half are splenectomized. Blood examinations are repeated one and two weeks later to determine the activity of the drug. Results for a number of current anti-malarial drugs tested in the model showed that drugs like pyrimethamine and primaquine possessed causal prophylactic activity, whereas others like chloroquine did not. More than five hundred compounds were screened by this system and the results indicated that it is a dependable method for primary screening. For some compounds, such as long-acting piperazine, atebriane, etc., it is necessary to make a further study in the simian malaria model recommended by Schmidt.

25. Qu, F. Y. et al. Experimental studies on orally administered long-acting antimalarials. II. Observations on therapeutic and prophylactic effects of hydroxypiperazine on rodent malaria. Acta Pharmaceutica Sinica, 1981, 16 (4) : 298 (In Chinese, with English abstract)

The results of experimental studies on the antimalarial effect of hydroxypiperazine against rodent malaria (Plasmodium berghei) showed that the median prophylactic dose (PD<sub>50</sub>) of hydroxypiperazine and its phosphate was much higher than that of piperazine. In infections with the normal P. berghei strain, the median curative dose (CD<sub>50</sub>) in mg (base)/kg body weight was 4.02-4.17 for hydroxypiperazine, 3.59-4.38 for its phosphate, 2.81 ± 0.25 for the citrate, 3.59 ± 0.14 for the hydroiodate, 4.29 ± 0.32 for the B-pamoate, 3.39 ± 0.14 for the hydrochloride, 3.36 ± 0.34 for the sulfate, and 3.76 ± 0.32 for the tartrate; while in infections with the resistant strain of P. berghei, the median curative dose (CD<sub>50</sub>) in mg (base)/kg body weight was 14.04 ± 0.41 for piperazine, 15.06 ± 1.13 for its phosphate, 11.8 ± 1.92 for the citrate, 12.09 ± 1.30 for the hydrochloride, and 11.13 ± 1.24 for the sulfate, these values being 3.3-4.2 times higher than those for infections with the normal strain.

Comparison of the therapeutic activities of hydroxypiperazine, piperazine and chloroquine at peak parasitaemia showed that the first two drugs had almost the same effectiveness, whereas chloroquine was less effective in terms of survival rate of the treated mice and infection rate of the erythrocytes.

26. The fourteenth Pharmaceutical Factory of Shanghai et al. The pharmacological and clinical research of a new drug, pyracoine phosphate, for the treatment of cerebral malaria. Chinese Journal of Internal Medicine, 1981, 20 (3) : 180 (In Chinese)

Pyracoine phosphate, 2-methoxy-6-chloro-9-(3',5'-bis (pyrrolidyl-1-methyl) 4'-hydroxy-anilino) acridine, is a new antimalaria drug synthesized in the People's Republic of China. In mice infected with Plasmodium berghei, the median curative dose (CD<sub>50</sub>) with a single intraperitoneal dose was 1.7 mg/kg body weight, while the median suppressive dose (SD<sub>50</sub>) was 1.3 mg/kg. In mice given a single intramuscular dose the median lethal dose (LD<sub>50</sub>) was 79.4 ± 6.0 mg/kg, while the LC<sub>50</sub> of chloroquine phosphate was 67.7 ± 4.48 mg/kg. No significant electrocardiogram (ECG) changes were seen in four dogs treated with pyracoine phosphate given in an intravenous dose of 20 mg/kg. Of three dogs receiving 30 mg/kg, two showed a prolonged P-R interval and broadened QRS in their ECG, and the third a ventricular arrhythmia. Abnormal ECG tracings returned to normal on the next day. Of the five dogs receiving 60 mg/kg, one died, and the other four showed a prolonged P-R interval, deepened S waves and a broadened QRS complex. These changes returned to normal one day later. All four dogs given chloroquine phosphate intravenously at the dose of 10 or 20 mg/kg as control died.

42 cases of cerebral malaria due to P. falciparum and 2 cases of P. vivax were treated with pyracoine phosphate. The total dose varied from 300 to 800 mg, being mostly 600 mg over three consecutive days. Intravenous therapy was given by dissolving 150 mg of the drug in 500 ml of 5-10% glucose saline. The criteria for cure were: (1) complete recovery of consciousness; (2) drop of the temperature to normal range; and (3) clearance of parasitaemia in thick smears for three consecutive days. All the patients were cured.

27. Liu, H. M. et al. Studies on the constituents of Qinghao (Artemisia annua L.). Acta Pharmaceutica Sinica, 1981, 16 (1) : 65 (In Chinese, with English abstract)

From Artemisia annua L., five crystalline compounds have been isolated besides arteannuin. On the basis of spectral data (UV, IR, NMR, MS) and physico-chemical constants, these compounds have been identified as: scopoletin; coumarin; quercetagetin-6, 7, 3', 4'-tetramethyl ether; quercetagetin-6, 7, 4'-trimethyl ether; and artemetin.

It is the first time that coumarin, quercetagetin-6, 7, 4'-trimethyl ether and artemetin have been isolated from this drug.

28. Zhang, Y. Z. Medicinal history and market survey of the Chinese drug "Chinghao" (Qinghao). Chinese Pharmaceutical Bulletin, 1981, 16 (4) : 5 (In Chinese)

Qinghao, a popular medicinal herb, had been used for the treatment of malaria in ancient China, as recorded in "Zhou Hou Bei Ji Fang" by Ge Hong 281-340 (Jin dynasty). In "Ben Cao Gong Mu" written by Li Shi-zhen in 1578 (Ming dynasty), descriptions of the morphology and properties of both Qinghao and Huanghuahao were given. Investigations into the geographical distribution and species identification of Artemisia were carried out and revealed that six species were commercially used, namely, Artemisia annua L. (Huanghuahao), A. apiacea Hance (Qinghao), A. scoparia Waldst & Kitaib (Zhumaohao), A. capillaris Thunb (Yinchenhao), A. japonica Thunb (Muhao) and A. eriopoda Bunge (Nanmuhao); sometimes they are marketed under the unique name "Qinghao". Actually, Huanghuahao (A. annua L.) possesses a pronounced antimalarial activity, while the effectiveness against malaria of Qinghao (A. apiacea Hance) itself still needs to be tested. Huanghuahao is widely distributed in China, whereas the distribution of Qinghao is rather limited. It is misleading to call Artemisia annua "Qinghao".