WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 1, 819-828. Review Article ISSN 2277– 7105

A SYSTEMATIC REVIEW ON PHYTOMEDICINAL TREATMENT OF MALARIA

Dr. Mohd. Wasiullah[1], Piyush Yadav*[2], Mohd. Furquan[3] and Mohit Vishwakarma[4]

[1]Principal, Dept. of Pharmacy, Prasad Institute of Technology, Jaunpur (222001) U.P, India.

[2]Principal, Dept. of Pharmacy, Prasad Polytechnic, Jaunpur (222001) U.P, India.

[3]Dept. of Pharmacy, Prasad Institute of Technology, Jaunpur (222001) U.P, India.

[4]Assistant Professor, Dept. of Pharmacy, Prasad Institute of Technology, Jaunpur (222001) U.P, India.

Article Received on
14 Nov. 2022,
Revised on 04 Dec. 2022,
Accepted on 24 Dec. 2022
DOI: 10.20959/wjpr20231-26730

***Corresponding Author**
Piyush Yadav
Principal, Dept. of Pharmacy, Prasad Polytechnic, Jaunpur (222001) U.P, India.

ABSTRACT

Malaria is a devastating and very infectious disease which is known to cause around one million deaths per annum worldwide. This is a life-threatening disease which is mostly prevalent in Africa. Development of drug resistance by malarial parasites to the conventional anti-malarial treating drugs has arisen the exploration of herbal medicines as an alternative. Also, the increasing rate of the use of herbal anti-malarial remedies in combination with the conventional anti-malarial treating drugs has inspired researchers to validate any herb and drug interaction effects. This present review paper covers some of natural compounds from plants with anti-plasmodial and anti-malarial properties, belonging to the class of terpenes, limonoids, flavonoids, chromones, xanthones, anthraquinones, miscellaneous and related compounds.

KEYWORDS: Malaria, anti-malarial, anti-plasmodial, herbal medicine, drug resistance.

INTRODUCTION

The disastrous and infectious disease, malaria, is responsible for causing deaths of millions worldwide especially Africa.[1] According to WHO estimation in 2015 there were 212 million cases of malaria and 4.29 lakhs deaths worldwide. Charles Louis Alphonse Laveran, a French army surgeon, was the first to observe malaria parasite in a patient's blood who was suffering from malaria on 6 November 1880. He was awarded Nobel prize in 1907.[2] Way back in 1947 of a population of 330 million nearly 75 million people were estimated to be suffering

from malaria which resulted in death of people about 0.8 million every year.[3] There are 4 different species of Plasmodium which is responsible for causing malaria in humans; Plasmodium Falciparum, Plasmodium Vivax, Plasmodium Ovale and Plasmodium Malariae. The most widespread and severe disease is caused by P. Falciparum, which infects the liver before destroying RBCs of the mammalian host. The clinical manifestations happens at the erythrocytic stage and induced fever, chills, prostation, anaemia, delirium, metabolic acidosis, and multiple organ system failure, which may be followed by coma or death.[4-6] Due to increasing problems of drug resistance towards plasmodium species there seems to be an urgent need to develop new lead compounds to treat malaria.[7] Ethnopharmacology serves as one of the best sources to find a plant molecule which can be used as a lead compound for preparing antimalarials.[8] About 80% of the world populations still rely on the use of plants based traditional health care products for there health care purposes.[9] Previously, molecules including quinine, artemisinin and many others have been purified from herbal drugs.[10]

Quinine, an aminoquinoline alkaloid was isolated from cinchona species (Rubiaceae) bark in 1820 by Pelletier and Caventou, is one of the oldest and important antimalarial drugs and is used today also. It is an effective principle against P. Falciparum after World War 2, it was considered responsible for development of synthetic antimalarial drugs belonging to the classes of 4- and 8-aminoquinolines, such chloroquine (1940) and Primaquine (1952) among others. Until recently, chloroquine was the only drug which was used for the treatment of malaria.[11-12] The observation of drug resistance by P. falciparum strain started since 1960, particularly of chloroquine has made the treatment of malaria largely problematic in virtually or malarial regions of the world.[13] Several researchers have dedicated their effects in the development of new active compounds such as from artemisinin, as an alternative to chloroquine. Currently no single drug is effective in multiple drug resistant malaria treatment and hence an effective combination therapy includes artemisinin derivative such as artesunate, or mixtures with other drugs such as atovaquone-proguanil combination Malarone.[13-14] Unfortunately first report of drug resistance to artemisinin- derivatives[15] and to drug combination therapies[16] have appeared already.

Hence, in the absence of functional safe ana widely available malaria vaccine, efforts have been made to develop new anti-malarial drugs which are continued to be in use now. The main rational of this review is to analyse the conventional and natural products which can be

used as lead for future novel antimalarial drugs. In this review, an attempt has been made to highlight the anti-plasmodial properties of antimalarial plants from various sources.

➢ LIFE CYCLE OF P. FALCIPARUM

Plasmodium species which is known for causing malaria belong to phylum Apicomplexa. All members of this phylum are obligate intracellular protozoal parasite.[17] The malarial parasite has a very complex life-cycle, wherein it require host and vector to complete its life-cycle.[18-19]

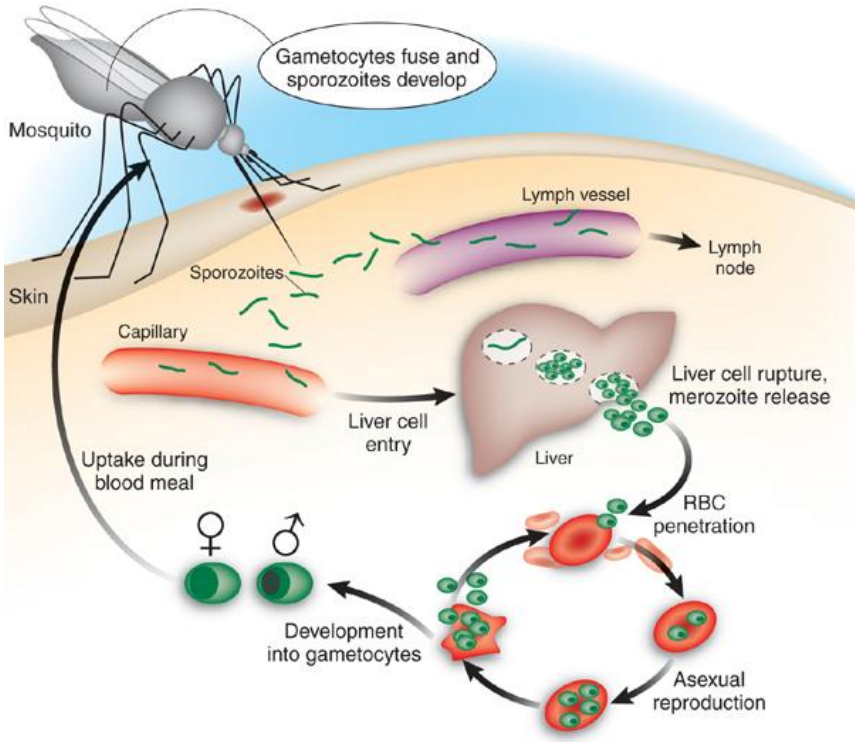

Figure 1. Schematic life cycle of malaria in humans. Sporozoites are injected into human dermis through the bite of infected *Anopheles* mosquito. After inoculation, sporozoites migrate to liver cells to establish the first intracellular replicative stage. Merozoites generated from this exoerythrocytic phase then invade erythrocytes (RBCs), and it is during this erythrocytic stage that severe conditions of malaria occur. The life cycle is completed when sexual stages (gametocytes) are ingested by a mosquito. Some sporozoites deposited in the skin eventually penetrate capillaries or lymph vessels. Those entering the lymph vessels will penetrate lymph vascular endothelial cells in lymph nodes to establish a lymph node form, which appears not to continue the life cycle - but may be significant in priming an immune response. Adapted and reproduced by permission from Macmillan Publishers Ltd.

Kaur and co-authors published a review in 2009 which focussed on the anti-malarial compounds discovered during 1998-2008 from all natural sources including crude plant, and marine extracts. A total of 266 anti-plasmodial natural products pertaining to the classes of alkaloids, terpenes, quassinoids, flavonoids, limonoids, chalcones, peptides, xanthones, quinones, coumarins and miscellaneous compounds, as well as 37 promising semi-synthetic antimalarials were listed in the compilation.[20]

➢ ANTIMALARIAL DRUGS AND DRUG RESISTANCE

The worsening problem of drug resistance has caused many of the antimalarials in use ineffective, thus increasing the rate of morbidity and mortality.[21]

1. **QUININE:** It was discovered in 17th century. Cinchona tree contains quine which was associated with its use as antimalarial back from 1600s. During those days, it was called as "Jesuits' bark", "cardinal's bark", or "sacred bark".[22] It kills the malarial parasite by causing the food vacuole to swell thus leading to increase in the granularity of cell and lastly result in cell lyses. It took too long for the parasite to gain resistance to quinine.

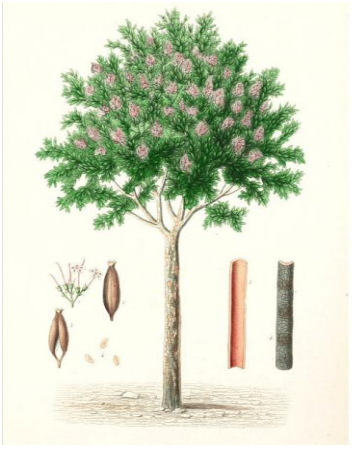

Fig.1.1- Cinchona tree and bark.

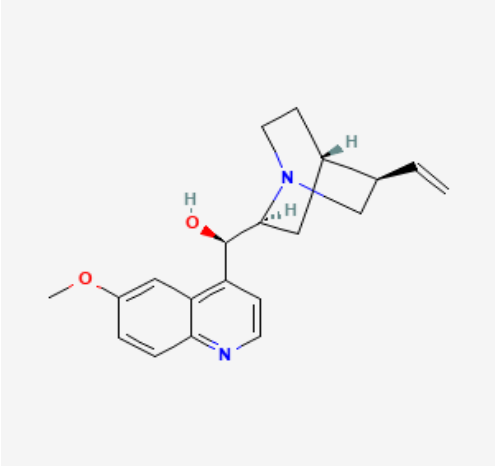

Fig.1.2- Quinine chemical structure.

2. **CHLOROQUINE:** It does not allow the hematin to detoxify in the digestive vacuoles of the parasite thus causing toxicity to it, which leads to the parasite death. The resistance to chloroquine is due to mutation that cause within PfCRT (Plasmodium falciparum chloroquine resistance) and it is studied that the mutation has occurred at the position 76 (K76T).[23]

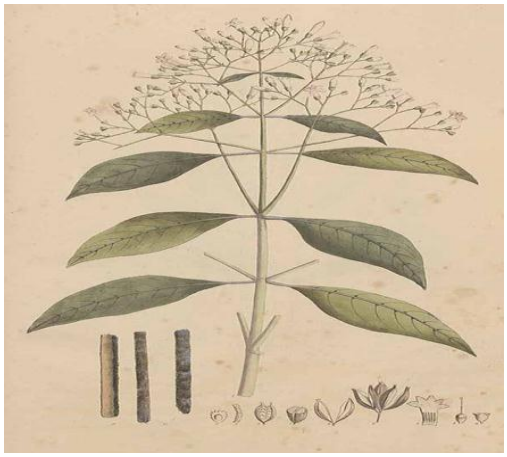

Fig.2.1- Cinchona plant and bark.

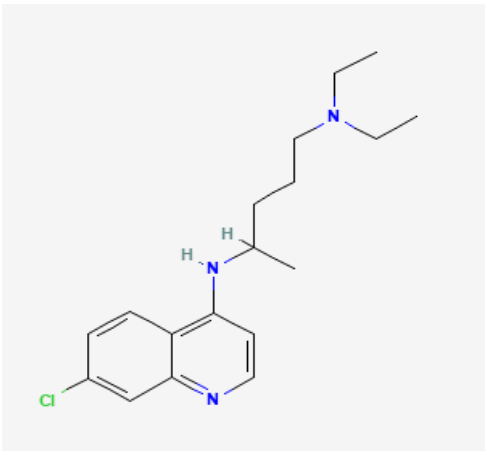

Fig.2.2- Chloroquine chemical structure.

3. **ARTEMISININ:** It is as recent and widely used antimalarial drug which is used as a first line treatment for P. falciparum and has also gained drug resistance in many parts of the world, especially Southeast Asia. Artemisinin, a tetracyclic 1,2,4-trioxane containing an endoperoxide bridge, is the key pharmacophore of this drug.[24] This drug is obtained from the herb sweet wormwood selective anti-cancer properties to some extract.

All antimalarial drugs are anti-pyretic in nature but not all anti-pyretic are antimalarials. Keeping this in mind, one can screen plants possessing antipyretic activity to check its antimalarial effectiveness.

Fig.3.1- Artemisia plant.

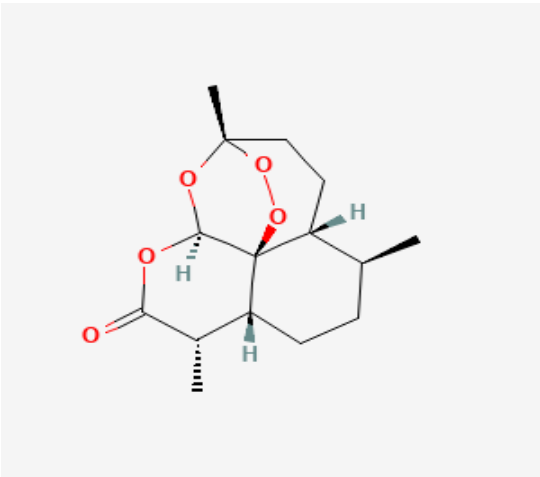

Fig.3.2- Artemisinin chemical structure.

In table 1, a list of some plants possessing antipyretic along with antimalarial properties are shown.

Table 1: List of plants reported to possess antimalarial and antipyretic activity.

S. No.	Plant Name	Family	Activity	Reference
1	Abrus precatorius L	Fabaceae	Anti-malarial	[25]
2	Acanthus montanus	Acanthaceae	Anti-pyretic	[26]
3	Adansonia digitata	Bombacaceae	Anti-pyretic	[27]
4	Aegle marmelos	Rutaceae	Anti-pyretic	[28]
5	Alafia barteri	Apocynaceae	Anti-malarial	[29]
6	Albizia anthelmintica Brongn.	Fabaceae	Anti-malarial	[30]
7	Allium sativum L.	Alliaceae	Anti-malarial	[31]
8	Aloe vera L.	Xanthorrhoeaceae	Anti-malarial	[30]
9	Amaranthus hybridus	Amaranthaceae	Anti-malarial	[30]
10	Amaranthus spinosus	Amaranthaceae	Anti-malarial	[32]

Table 2: Antimalarial activity of plant metabolites.

Plant	Family	Metabolite	Compound	Reference
Piptadenia pervillei Vatke	Leguminosae	Phenolic derivatives Flavonoid derivatives	(+)-catechin 5-gallate (+)-catechin 3-gallate	[33]
Bauhinia purpurea L.	Leguminosae	Flavonoid derivatives	Demethoxymatteucinol	[34]
Artocarpus rigidus	Moraceae	Flavonoids	Artonin F Cycloartobiloxanthone	[35]
Artocarpus champeden	Moraceae	Prenylated flavones Prenylated flavonoids	Artocarpones A Artocarpones B Artonin A Cycloheterophyllin Artoindonesianin R Heterophyllin Heteroflavanone C Artoindonesianin A-2	[36]
Garcinia polyantha Oliv.	Clusiaceae	Xanthone	Garciniaxanthone Smeathxanthone A Smeathxanthone B Chefouxanthone	[37]
Phyllanthus niruri L.	Euphorbiaceae	Coumarin	1-O-galloyl-6-O-luteoyl-a-D-glucose	[38]
Punica granatum L.	Lythraceae	Tannins	Gallagic acid	[39]
Cannabis sativa L.	Cannabaceae	Quinones	5-acetoxy-6-geranyl-3-npentyl- 1,4-benzoquinone	[40]
Bauhinia purpurea L.	Leguminosae	Quinones	Bauhinoxepin I Bauhinoxepin J	[41]
Artemisia gorgonum Webb	Asteraceae	Terpenoid (germacranolide)	Hanphyllin	[42]

CONCLUSION

Malaria has continued to be a burden to mankind and now it is the exact time to control and eradicate this menacing disease. One would have to thoroughly understand the biology of malaria and parasite to develop an effective medicine and its cure. The is only hope now, is to find a lead compound from plants. There are many plant species which have been identified for their antimalarial properties. There are more optimistic properties perspective on continuing investigation of more antimalarial property bearing plant for the treatment of malaria.

REFERENCES

1. Miller, L.H., Ackerman, H.C., Su, X.-.Z., Wellems, T.E., 2013. Malaria biology and disease pathogenesis: insights for new treatments. Nature Medicine, 19: 156–167.
2. Tren, R., 2002. Working papers series malaria and climate change.
3. Kumar, A., Valecha, N., Jain, T., Dash, A.P., 2007. Burden of malaria in India: retrospective and prospective view. American Journal of Tropical Medicine and Hygiene, 77: 69–78. 77/6_Suppl/69.
4. Fidock, D.A.; Rosenthal, P.J.; Croft, S.L.; Brun, R.; Nwaka, S. Antimalarial drug discovery: efficacy models for compound screening. *Nat. Rev. Drug Discov*, 2004; *3:* 509-520.
5. Deprez-Poulain, R.; Melnyk, P. 1,4-Bis(3-aminopropyl)piperazine libraries: from the discovery of classical chloroquine-like antimalarials to the identification of new targets. *Comb. Chem. High Throughput Screen*, 2005; *8:* 39-48.
6. Jones, M.K.; Good, M.F. Malaria parasites up close. *Nat. Med.*, 2006; *12:* 170-171.
7. Bozdech, Z., Ferreira, P.E., Mok, S., 2015. A crucial piece in the puzzle of the artemisinin resistance mechanism in Plasmodium falciparum. Trends in Parasitology, 31: 345–346.
8. Bero, J., Fr_ed_erich, M., Quetin-Leclercq, J., 2009. Antimalarial compounds isolated from plants used in traditional medicine. Journal of Pharmacy and Pharmacology, 61: 1401–1433.
9. Teklehaymanot, T., Giday, M., 2007. Ethnobotanical study of medicinal plants used by people in Zegie Peninsula, Northwestern Ethiopia. Journal of Ethnobiology and Ethnomedicine, 3: 12.
10. Wells, T.N., 2011. Natural products as starting points for future anti-malarial therapies: going back to our roots. Malaria Journal, 10: S3.

11. Saxena, S.; Pant, N.; Jain, D.C.; Bhakuni, R.S. Antimalarial agents from plant sources. *Curr. Sci.*, 2003; *85*: 1314-1329.
12. Viegas Júnior, C.; Bolzani, V.S.; Barreiro, E.J. Os produtos naturais e a química medicinal moderna. *Quím. Nova*, 2006; *29*: 326-337.
13. Winter, R.W.; Kelly, J.X.; Smilkstein, M.J.; Dodean, R.; Bagby, G.C.; Rathbun R.K.; Levin, J.I.; Hinrichs, D.; Riscoe, M.K. Evaluation and lead optimization of anti-malarial acridones. *Exp. Parasitol*, 2006; *114:* 47-56.
14. Taylor, W.R.; White, N.J. Antimalarial drug toxicity: a review. *Drug Saf.*, 2004; *27:* 25-61.
15. Jambou, R.; Legrand, E.; Niang, M.; Khim, N.; Lim, P.; Volney, B.; Ekala, M.T.; Bouchier, C.; Esterre, P.; Fandeur, T.; Mercereau-Puijalon, O. Resistance of *Plasmodium falciparum* field isolates to *in vitro* artemether and point mutations of the SERCA-type PfATPase6. *Lancet*, 2005; *366*: 1960-1963.
16. Wichmann, O.; Muhlen, M.; Grub, H.; Mockenhaupt, F.P.; Suttorp, N.; Jelinek, T. Malarone treatment failure not associated with previously described mutations in the cytochrome *b* gene. *Malaria J.*, 2004; *3:* 1-3.
17. O'Donnell, R.A., Blackman, M.J., 2005. The role of malaria merozoite proteases in red blood cell invasion. Current Opinion in Microbiology, 8: 422–427.
18. Schmidt, C.Q., Kennedy, A.T., Tham, W., 2015. More than just immune evasion: hijacking complement by Plasmodium falciparum. Molecular Immunology, 67: 71–84.
19. Bruce-Chwatt, L.J., 1987. Malaria and its control: present situation and future prospects. The Annual Review of Public Health, 8: 75–110.
20. Kaur, K.; Jain, M.; Kaur, T.; Jain, R. Antimalarials from nature. *Bioorg. Med. Chem.*, 2009; *17*: 3229-3256.
21. Newton, P.N., Caillet, C., Guerin, P.J., 2016. A link between poor quality antimalarials and malaria drug resistance? Expert Review of Anti-infective Therapy, 14: 531–533.
22. Achan, J., Talisuna, A.O., Erhart, A., Yeka, A., Tibenderana, J.K., Baliraine, F.N., Rosenthal, P.J., D'Alessandro, U., 2011. Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. Malaria Journal, 10: 144.
23. Djimde, A., Doumbo, O.K., Cortese, J.F., Kayentao, K., 2001. A molecular marker for chloroquine-resistant falciparum malaria. The New England Journal of Medicine, 344: 257–263.
24. Antoine, T., Fisher, N., Amewu, R., O'Neill, P.M., Ward, S.A., Biagini, G.A., 2014. Rapid kill of malaria parasites by artemisinin and semi-synthetic endoperoxides involves

ROS-dependent depolarization of the membrane potential. Journal of Antimicrobial Chemotherapy, 69: 1005–1016.

25. Bickii, J., Tchouya, G.R.F., Tchouankeu, J.C., Tsamo, E., 2007. Antimalarial activity in crude extracts of some Cameroonian medicinal plants. The African Journal of Traditional, Complementary and Alternative Medicines, 4: 107–111.
26. Asongalema, E.A., Foyet, H.S., Ekobo, S., Dimo, T., Kamtchouing, P., 2004. Antiinflammatory, lack of central analgesia and antipyretic properties of Acanthus montanus (Ness) t. Anderson. Journal of Ethnopharmacology, 95: 63–68.
27. Ramadan, A., Harraz, F.M., El-Mougy, S.A., 1994. Anti- inflammatory, Analgesic and antipyretic effects of the fruit pulp of Adansonia digitata. Fitoterapia, LXV: 418–422.
28. Arul, V., Miyazaki, S., Dhananjayan, R., 2005. Studies on the anti-inflammatory antipyretic and analgesic properties of the leaves of Aegle marmelos Corr. Journal of Ethnopharmacology, 96: 159–163.
29. Lasisi, A.A., Olayiwola, M.A., Balogun, S.A., Akinloye, O.A., Ojo, D.A., 2016. Phytochemical composition, cytotoxicity and in vitro antiplasmodial activity of fractions from Alafia barteri olive (Hook F. Icon)-Apocynaceae. Journal of Saudi Chemical Society, 20: 2–6.
30. Soejarto, D.D., Gyllenhaal, C., Kadushin, M.R., Southavong, B., Sydara, K., Bouamanivong, S., Xaiveu, M., Zhang, H.-J., Franzblau, S.G., Tan, G.T., Pezzuto, J.M., Riley, M.C., Elkington, B.G., Waller, D.P., 2012. An ethnobotanical survey of medicinal plants of Laos toward the discovery of bioactive compounds as potential candidates for pharmaceutical development. Pharmaceutical Biology, 50: 42–60.
31. Ahmed, E.-H.M., Nour, B.Y.M., Mohammed, Y.G., Khalid, H.S., 2010. Antiplasmodial activity of some medicinal plants used in Sudanese folk-medicine. Environmental Health Insights, 4: 1–6.
32. Moshi, M.J., Otieno, D.F., Weisheit, A., 2012. Ethnomedicine of the Kagera Region, north western Tanzania. Part 3: plants used in traditional medicine in Kikuku village, Muleba District. Journal of Ethnobiology and Ethnomedicine, 8: 14.
33. Ramanandraibe, V., Grellier, P., Martin, M.-T., Deville, A., Joyeau, R., Ramanitrahasimbola, D., Mouray, E., Rasoanaivo, P., Mambu, L., 2008. Antiplasmodial phenolic compounds from Piptadenia pervillei. Planta Medica, 74: 417–421.
34. Boonphong, S., Puangsombat, P., Baramee, A., Mahidol, C., Ruchirawat, S., Kittakoop, P., 2007. Bioactive compounds from Bauhinia purpurea possessing antimalarial,

antimycobacterial, antifungal, anti-inflammatory, and cytotoxic activities. Journal of Natural Products, 70: 795–801.

35. Namdaung, U., Aroonrerk, N., Suksamrarn, S., Danwisetkanjana, K., Saenboonrueng, J., Arjchomphu, W., Suksamrarn, A., 2006. Bioactive constituents of the root bark of Artocarpus rigidus subsp. rigidus. Chemical and Pharmaceutical Bulletin, 54: 1433–1436.
36. Widyawaruyanti, A., Subehan, Kalauni, S.K., Awale, S., Nindatu, M., Zaini, N.C., Syafruddin, D., Asih, P.B.S., Tezuka, Y., Kadota, S., 2007. New prenylated flavones from Artocarpus champeden, and their antimalarial activity in vitro. The Journal of Natural Medicines, 61: 410–413.
37. Lannang, A.M., Louh, G.N., Lontsi, D., Specht, S., Sarite, S.R., Fl€orke, U., Hussain, H., Hoerauf, A., Krohn, K., 2008. Antimalarial compounds from the root bark of Garcinia polyantha Olv. Journal of Antibiotics, 61: 518–523.
38. Subeki, Matsuura, H., Takahashi, K., Yamasaki, M., Yamato, O., Maede, Y., Katakura, K., Kobayashi, S., Trimurningsih, Chairul, Yoshihara, T., 2005. Anti-babesial and antiplasmodial compounds from Phyllanthus niruri. Journal of Natural Products, 68: 537–539.
39. Reddy, M., Gupta, S., Jacob, M., Khan, S., Ferreira, D., 2007. Antioxidant, antimalarial and antimicrobial activities of tannin-rich fractions, ellagitannins and phenolic acids from Punica granatum L. Planta Medica, 73: 461–467.
40. Radwan, M.M., ElSohly, M.A., Slade, D., Ahmed, S.A., Wilson, L., El-Alfy, A.T., Khan, I.A., Ross, S.A., 2008. Non-cannabinoid constituents from a high potency Cannabis sativa variety. Phytochemistry, 69: 2627–2633.
41. Boonphong, S., Puangsombat, P., Baramee, A., Mahidol, C., Ruchirawat, S., Kittakoop, P., 2007. Bioactive compounds from Bauhinia purpurea possessing antimalarial, antimycobacterial, antifungal, anti-inflammatory, and cytotoxic activities. Journal of Natural Products, 70: 795–801.
42. Ortet, R., Prado, S., Mouray, E., Thomas, O.P., 2008. Sesquiterpene lactones from the endemic Cape Verdean Artemisia gorgonum. Phytochemistry, 69: 2961–2965.