

<u>International Journal of TROPICAL DISEASE & Health</u>
2014_IJTDH_8920
Understanding Of Malaria And Its Therapeutic Regimens – The Way Forward
Review Article

ESSENTIAL References.

The paper is about Nigeria. The caption is all about global ! Hence some elaboration/expansion is necessary.

The matter as in *italics* are to be considered for induction (marked as **). Approximate places of induction have also been indicated. The References have been provided accordingly.

INTRODUCTION

*** Afro Asian Strains Differ. Authors may kindly consider to bring this aspect to light as because almost all reviews have made no mention thus far. It is as an important aspect. THEREFORE,*

A Table showing the nomenclatures (as apportioned by WHO) of various Resistant and new emergent Poly-morphic strains Africa – Asia – Latin America (select short table – with hyper link to a more detailed and larger one - WILL be very useful for world wide ref & citations)

*** Malaria has also been articulated in the very ancient - few millennia old texts - and erudite Hindu schools of medicine and which all have remained encrypted in Sanskrit (indian national lingua) and hence has been missed by the African and even by the Oriental scientific community [R1-to-4]. And, the ancient Hindu medicine specialist Specially, Madhava Kar defines malarial symptoms via the phones kampa (rigor); trutiyaka (tertian) and chaturthaka (quartan), among other sub-types of fevers (supporting information), which all types are also noted pan globally.*

R1- Atharva Veda Samhita, "Medicine Chapter as Cited in P. Sen, 1907," Journal of the Asiatic Society, 1907, pp. 11-12.

R2- Charak Samhita c.4th A.D., of Agnivesa, Bramhanand Tripathy ed., 2 Vols. Chaukhamba Surabharati Prakashan, Varanasi, 1973. AND Charak Samhita of Agnivesh, 2 Vols., Ed. Kashinath Sastri and Gorakhnath Chaturvedi, Chowkhamba Vidyabhavan, Varanasi, 1969. See also Ayurveda; Palm leaf mss., (Iron stylus scripted, c.18th edition of original c.4th A.D), No. Ay-435B, Odisha State Museum, Bhubaneswar - India.

R3- Chikitsa Manjaree (separate Eds., by Jagannath Das & Gopinath Sadhangi), Palm Leaf Mss. c.1800 Ed. of earlier original work dt. c.8th A.D (Iron stylus scripted; Original Mss), No. Ay-136 & 162. India: Orissa State Museum, Bhubaneswar, India..

R4- Acharya Priyabrata Sharma's, 'Dravyaguna Vigyana' (science of medicinal qualities), Chowkhamba Publications, Benaras Hindu University, 1980, India

**** We also note very Large Scale National Efforts, involving national exchequers and national priority programs spanning long periods with sub-continent wide swaths specially India (1Billion + population) which is among the most resourceful of the year round malaria infected nations [R1-2].**

R1- National Malaria Control Program. Govt. of India. Ministry of Health. 1953.
Available. mohfw.nic.in/WriteReadData/l892s/Chapter06-93270370.pdf

R2- National Malaria Eradication Program. 1958.
Available : whoindia.org/LinkFiles/Malaria_Country_Profile-Malaria.pdf

**** We also note unique mini and small scale (yet very effective) Public – Private Initiatives in the remote of the rural country side [R1]**

R1- Express 1-15th May, 2006. Pharma, Bombay, Fortnightly,
<http://www.expresspharmaonline.com/20060515/research02.shtml>

Line No. 150 : Attention !

C. Laveran's - may be quoted *ad-verbatim* – for the benefit of record dissemination (only if available).
Few lines from his source or a scanned copy his hand written note (then super best) – only if possible.

Around Line No. 150 OR around Line No. 231

**** Hepatocyte stage studies (of the parasites) is gradually yielding never before information as part of evidence based studies by use of very imaginative methods even involving extra mural specialist [R1].**

[R1] Sania S, et al. Host Cell Transcriptional Profiling During Malaria Liver Stage Infection Reveals A Coordinated And Sequential Set Of Biological Events, *Genomics*. 2009;10:270.

Section 2.5 : Around line 281-85.

**** From time to time specialised reviews have also been made about pathophysiology [R1]. In this study we review the full gamut of issues. We also focus on central tropical Africa (Nigeria in particular, because we have long period expouser to ground Nigeria)**

R 1 - Clark & Cowden, The Pathophysiology of Pf Malaria, *Pharmacology & Therapeutics*, Vol. 5555 (2003), pp. 1 – 39.

Around Line. No. 356

**** Filed\pathological microscope's has a sterling role in Malaria detection & combat. It is considered as Gold standard by WHO. Rapid Detection Kits are no doubt handy yet suffer from the absence of Cold Chain. And, malaria is a malady of the moist and most of malaria infected geography has no un-interrupted electrical power (this includes even India) [R1].**

R1 - Bhattacharya Deepak, Relevance of economic field microscope in remote rural regions for concurrent observation of malaria & inflammation.

Advances in Infectious Diseases. 2012;2:13-18. doi:10.4236/aid.2012.21003.

**** New Drugs (and sources) having paradigm shift from concept to finish are being reported [R1; 2].**

R1 - Bhattacharya Deepak. *Punica granatum*'s dermis indicates anti-malarial therapeutics & prophylaxis, 4th Pan African Malaria Conference, **Multilateral Initiative on Malaria**, Yaounde, Cameroon, 13–18 Nov.2005; No.183C, 195-96. No.183C. Available:

<http://www.mim.su.se/conference2005/eng/embargopress/MIM2005%20-%20Abstract%20book.pdf>.

R2- Dell'Agli, G. V. Galli, Y. Corbett, D. Taramelli, L. Lucantoni, A. Habluetzel, O. Maschi, D. Caruso, F. Gia- varini, S. Romeo, D. Bhattacharya and E. Bossisio, "An- tiplasmodial Activity of *Punica granatum* L. Fruit Rind," **Journal of Ethnopharmacology**, Vol. Vol. 125, No. 2, 2009, pp. 279-285.

doi:10.1016/j.jep.2009.06.025

**** Fruits and waste parts of fruit processing industry are now also being used as source for New Drugs and reported to have Wide Spectrum Efficacy [R1]**

R1- Dell' Agli M, Galli GV, Bulgari M, Basilico N, Romeo S, Bhattacharya D, Taramelli D, Bosisio E. Ellagitannins of the fruit rind of pomegranate (*Punica granatum*) antagonize *in vitro* the host inflammatory response mechanisms involved in the onset of malaria. **Malaria Journal**. 2010;9:208.

doi:10.1186/1475-2875-9-208.

Around or after Line. No. 279

**** New Anti-Brain Malaria Drugs are also being researched/reported and being in clinical application mode [R1].**

R1 - Bhattacharya D. Punicalin And Punicalagin Fails Cerebral Malaria ? **American Journal of Tropical Medicine and Hygiene**. Oct. 2010 Abstract No. 709, (ses B); 83 (5-Supp): p. 72. At www.astmh.org/AM/Template.cfm?Section=Abstracts_and...cfm.

<http://www.mim.su.se/conference2005/eng/embargopress/MIM2005%20-%20Abstr>

The following as a new point : (post Line No. 279)

**** Cations (as buffers) & Ions in anomeric form (as efficacy upregulator) which all also jointly and severally (act as propulsion engine) are now also being explored in anti-malaria drug discovery efforts, which is a bold new concept [1].**

R1 - Bhattacharya D. Tannins, Ions, Cations & malariasis: observations & theory, **American Journal of Tropical Medicine and Hygiene**, Oct. 2007; Vol. 77, Abstract No. 5, p. 27.

As part of Introduction OR Discussions OR under head 'Alternative Medicine' :

**** Nations, societies and scientists world wide are noted to be going back to Mother Nature to seek new sterling Source to combat malaria safely and effectively, includes members of the conventional school of medicine [R1].**

R1 - Ameh SJ, Obiageri OO, Peace BC, Karnuis GS. Medical herbalism and herbal clinical research: a global perspective. **British Journal of Pharmaceutical Research**. 2011;1.4:99-123.

**** World wide there has also been a rise in the number of research journals dedicated to alternative medicines. Ref. 1, 2 & 3.**

1. www. Jor of Alternative Medicine.
2. www. NIH-CAM-USA.
3. www. Indian Jor of Ayurveda & numerous others.

**** New Discoveries relating to malaria prophylaxis; therapeutic and or community service are treated Apex International News. In other words everything about malaria is important.**

BBC World, South Asia, Tuesday, 24 October, 2000, 12:16 GMT 13:16 UK
news.bbc.co.uk/2/hi/south_asia/988316.stm

Around Line No.296 and elsewhere as suitable

**** Successful inoculation by fleas and flies of other species were always suspected, and now reports have started trickling in, which indicates Multiple Vectors or on the horizon is the stark reality of cross species carriers [R1].** The add-on problem is that some of alleged neo vectors are diurnal fliers and meal seekers while some have a 24hr cycle.

R1 - Derua AY, Alifrangis M, Hosea KM, Meyrowitsch DW, Magesa SM, Pedersen EM, Simonsen PE. Change in composition of the *Anopheles gambiae* complex and its possible implications for the transmission of malaria and lymphatic Filariasis in Ne Tanzania. **Malaria Journal**. 2012;11:pp.188.
[doi:10.1186/1475-2875-11-188](https://doi.org/10.1186/1475-2875-11-188).

**** Malaria and Typhoid co-exists with malaria dominating a clinical presentation (at patient's 1st report). On treatment of malaria the patient lapses into acute phase typhoid – being misinterpreted as Brain Malaria leading to SOS calls for MDT (anti-malarias & antibiotics) – which is unwarranted, is deleterious and has lot much (even lingering) side effects [x,y]. Concurrent use are reported to cause 'cardiac failure'; alert has been issued [z]**

X - *Advances in infectious Diseases*. 2012;2:13-18. [doi:10.4236/aid.2012.21003](https://doi.org/10.4236/aid.2012.21003).

Y - *British Journal of Pharmaceutical Research*, 3(1): 54-77, 2013.

Z - MIMS- Monthly Index of Medical Specialties, Ref. Book for Clinicians, India,31.5,May-2011, p.15.

Around Line 328 :

****** *Co-infection is now a new emerging problem that is on-the horizon inter-continentially [R1 & 2]. Even poly infections and \ cum infestations are being reported even from resourceful fast developing nations [R3]*

R1 - NIH- National Institutes of Health Clinical Center, Medical Implications of Co-Infection

R2 - With Malaria and Filariasis Parasites, 2012; <http://clinicaltrials.gov/ct2/show/NCT00471666>.

R3 - *British Journal of Pharmaceutical Research*,3(1): 54-77, 2013. doi:10.1186/1471-2164-10-270.

Line No. 245-47 :

****** authors have to mention as to whether the gametocytes 'unite/coalesce/fuse' together while in human blood stream **or** whether such phenomena occurs post blood meal i.e., fusion/ex-\flagellation happens in the mid-gut stage of the anopheline ? PI explain a bit more sequentially. (ex-flagellation happens only in the case of anophelines (female) and NOT with anopheles (male) ? (please throw some light). Any other vector type also offer such/similar mechanism ?

Around Line. No. 255–

****** *Placental malaria is considered as very difficult to be treated / cleared and any chemotherapy (such as CQ & its group; ACTs & its derivatives; new poly-compounds viz., Synriam; etc) is fraught with complications. Therefore, pregnancy safe malaria drug is another requirement having high importance, and it has thus far been elusive [R1].*

[R1] - Prevalence and Risk factors for Placental Malaria in Nnewi, South east Nigeria;

International Journal Of Tropical Disease & Health, 2013-IJTDH Mss. No. 8365 ([in press](#)).

Section 2.6 - : Around Line No. 328

****** *Malarial parasite efficiently converts the Hb into Hemozoin (violet pigment) which is very stable; crystalline; toxic, reactive; necrolytic; and is held in malaria pathology pathway review [R1] as the principle agent that triggers the spiralling cascade of inflammatory syndrome which eventually gets to be called as 'complicated malaria' (involving numerous organs & physiological pathways) and subsequently as 'brain malaria' (involving extravasation in cerebral arteries). Thus hemozoin is the principal candidate that causes brain/cerebral malaria. It is very difficult to manage in pregnancy; anaemia; thrombocytopaenia; sickle cell. Malaria-Cancer-Endotoxemia have near identical clinical symptoms (particularly vis-a-vis inflammation) and any two of the trio do not occur jointly. Malaria is also a response pathology. The Indian new drug OMARIA is said to be very effective in down-turning hemozoin creation and in pro-hemozoin generation [R2]. Poly organ involvement also includes the thyroid gland – thereby involving the whole endocrine system, which rarely any other infestation does so early in the day [R3]. Hearing problems i.e., cochlear damage has attributed to conventional (allopathic) drugs [R4].*

R 1 - Prato M, Giribaldi G. Matrix Metalloproteinase-9 and Hemozoin: Wedding Rings for Human Host and Pf Parasite in Complicated Malaria. **Journal of Tropical Medicine**. 2011;1-11. doi:10.1155/2011/628438.

R 2 - **Malaria Journal**. 2010; Vol. 9, pp.208. doi:10.1186/1475-2875-9-208.

R3 - Hume J B. Enlargement Of The Thyroid Gland In Malaria. **The British Medical Journal**. Nov. 22, 1919, p.66r.

R4 – Toovey S, Jamieson A. Audiometric Changes (Neurotoxicity) Associated With The Treatment Of Uncomplicated Falciparum Malaria With Co-Artemether. **Transactions of the Royal Society of Tropical Medicine and Hygiene**. 2003;98.5:261-267. doi:10.1016/j.trstmh.2003.11.001.

Around Line. No. 341 –

****** *Placental malaria is normal if a pregnant contracts malaria (any species). It inflicts maternal anemia and complications for the fetus [R2]. Whereas prevention regime requires the pre-natal biology to be exposed to the toxic moieties of conventional drugs. Alternatives have remained elusive although they are frantically being searched for, worldwide. From such perspectives phyto based new sources are being reported [R3] which needs our attention.*

R2 - W H O., 'Lives at Risk: Malaria In Pregnancy'. Available at : www.who.int/feature/2003/04b/en.

R3 - Bhattacharya D., Orissa Malaria Research Indigenous Attempt – Prevention, **American Journal of Tropical Medicine and Hygiene**, Abstract No. 968, Vol. 171–No. 4, Oct. 2004, pp. 288. (Programme & Abstract Book). http://www.ajtmh.org/content/71/4_suppl/225.full.pdf+html

Around Line No. 376 :

****** *Rapid Detection Kits are also reporting falls negative & falls positives (apart from logistic costs and cold chain difficulties) [R1].*

R1 - Z. Tekeste, M. Workineh and B. Petros, "Comparison of Paracheck Pf ® Test with Conventional Light Microscopy for the Diagnosis of Malaria in Ethiopia," Asian Pacific Journal of Tropical Disease, Vol. 1, No. 3, 2012, pp. 1-3.

Also Around Line No. 376 :

****** *Another field level problem in drug resistant core endemic remote rural regions (sedate life style) is low parasite count – specially among the menopause and in general among the tribal geriatric groups. And, low count often fails to generate any signature in the RDT route. Binge drinking (specially the adulterated methyl alcohol) also fails/complicates RDT results even days post regain of sobriety (personal communication from Kpt, Odisha, India).*

Around Line No. 453 :

****** *Direct blood droplet test is now being tried (advanced stage) in India that will be very stable at tropical room temperature [R1]. For village level (part of India's altruistic humanistic administrative plan) service that is said to detect Pf & Pv & viral infestations in one go of only a few minutes (and an at home makeable technology i.e., people enabling).*

R 1 - Supporting information received from Oddisi Research Laboratory, India.

Around Line No. 465 :

****** *OMARIA (Orissa Malaria Research Indigenous Attempt) the Indian drug is reported to act via the NFkb terminal (by far seems to be the sole to do so; anti-parasite all stages including sporozoites and anti-gametocyte and is also anti-oxidant [R1 & R2]. Killing and clearing gametocytes will (solely) deliver 'transmission blockage'. And, such a drug as yet does not exist [R3]. Therefore, we are herein inclined to cite the Indian OMARIA (in order to bring it into focus).*

R1 - www. OMARIA – Anti malarial.

R2 - www. OMARIA – A Novel anti-malaria U-Tube.

R3 - Peatey L C, Didier L, Donald LG, Katharine RT. Anti-malarial Drugs. How effective are they against *Plasmodium falciparum* gametocytes? **Malaria Journal**, 2012;11:34 doi:10.1186/1475-2875-11-34.

Around Line No. 575 :

****** *While all conventional therapies use alkaloids which all are also chemotherapy; herbal medicaments may have an admixture. Interestingly, OMARIA the anti-malarial (said to be effective against Pf & Pv) uses ellagic acid and tannins (which are non- alkaloids and also non-chemotherapy (supporting information). Interestingly, obstetric and gynec clinicians opine that alkaloids have deleterious effect on the placental parynchema, and whereas mild-acids and specially ellagi-tannins seem to up-regulate healthy conditions at post partum (borrowed information – from anonymous sources). Thus we see workers across the globe are making intent efforts to combat malariasis effectively sans side effect.*

****** *An India Pharma news letter [R1] reports that research relating to malaria has the potential to because critical technology, has a very large employment base (diffused across the globe) and to attract large amounts of public money. Such indo averments was followed by call for involvement and investments under public private enterprise – having various nomenclature [R 2-to-5]. Even, year round cold/sub Arctic climate countries have got involved via Bio-metric Applications by seeking to rope in unrelated participants from Diffused Centers [R6].*

[R1] Drug One, Why Fight Malaria ? Chandigarh, India, May 2007, Vol.2, Issue-9, pp.30 & 36

[R2] White House. President's Malaria Initiative. 2006-07; Accessed 17-12-2012. Available. <http://georgewbush-whitehouse.archives.gov/infocus/malaria/>.

[R3] UNICEF. White House Summit on Malaria, New York, 2006.
Available: http://www.unicef.org/health/index_37773.html.

[R4] Bill & Milinda Gates Foundation. Grand Challenges in Global Health, 2008.
Available: <http://www.grandchallenges.org/explorations/Pages/introduction.aspx>.

[R5] GFATM. The Global Fund to Fight Aids, Tuberculosis and Malaria, 2010.
Available: www.theglobalfund.org/.

[R6] University College-Dublin.
Available www.fightmalaria.org/. UC-Dublin-2012.

In Section 2.8.2 (post Line No. 592)

****** *All present conventional anti-malarial drugs belong to the family of Chemotherapy. Non pass the stringent MRC-5 cell tests. Alone artemisinin passes such test. However, it has a very short plasma life and hence is of no use (virtually nil therapeutic index). In order to make it useful, a adamantin ring is engineered around it. The adamantin is quite toxic and also is a stable compound. Thus all ACTs are toxic in general and also cytotoxic to dermis; epithelial cells; hepatocytes; and to fetal tissues at development phase in particular. In-vitro cytotoxicity tests are being conducted on all new drugs & sources; even with comparative studies [R1]. In other words, all-anti-cancer drugs are also anti-malarials (albeit hyper potent). Even anti-gut protozoals (Tinidazole; Metronidazole; Albendazole) also help in malaria clearance and have synergic efficacy with conventional & herbal anti-malarials. Cancer drugs are not used directly because even falciparum is an ultra susceptible creature and in-order to protect itself it houses into the RBC. This is because the human defense mechanism is least oriented towards own RBCs. And, malariasis is always associated with anemia, erythrolysis and cancer drugs also cause anemia and acute erythrolysis – apart other deleterious effects.*

R1 - Soh PN, Witkowski B, Olagnier D, Nicolou LM, Alvarez MCG, Berry A. et al. In Vitro And In Vivo Properties Of Ellagic Acid In Malaria Treatment, Antimicrob Agents Chemotherapy. 2009, Vol. 53(3), pp.1100-1106. doi:10.1128/AAC.01175-08.

Around Line. No. 596.

****** *From Asia (Myanmar in particular) has come the user application knowledge (socio-cultural medicine) of artimessia annua which paved the way for ringing by a stable-toxic moiety 'the adamantin' of the otherwise labile\ unstable artmesinin to arrive at the ACT group of therapeutics. India has reported a pioneering effort titled "Fight Malaria at Home" [R1] which is also paving the way to Drug Discovery albeit with a paradigm shift having a bottom up model.*

Bhattacharya, Deepak. Fight Malaria at Home: Therapeutic and Prophylaxis Clinical Data, **Asian Pacific Journal of Tropical Disease**, Vol. 1(2), 2011, pp. 142-49.
doi: 10.1016/S2222-1808(11)60055-8. <http://www.apitcm.com/zz/2011jun/13.pdf>

****** Global meteorology do not recognize national or even continental boundaries. It is now being discussed that Malaria can Cross Continent via Meteorological routes and pathways [R1]. It is also being articulated as Malaria Meteorology, and even meteorologists are getting involved by the day.

[R1] Bhattacharya, Deepak. et.al., **British Journal of Pharmaceutical Research**, 3(1): 54-77, 2013. doi:10.1186/1471-2164-10-270.

Around Line No. 619 :

****** Most of the medicaments have developed resistance. At clinical level resistance registers as swings in other words, a given dose-dose regimen yields variable results even between two at-par patients having near identical pathological load and clinical symptoms. This is known as 'swing'. Artemisinin is therefore considered as the control in drug discovery (has the least swing – in vitro). A drug having wider swing will not be relied upon by the treating clinicians (as high/unpredictable swing is fraught with grave prognosis in acute cases). And researches in Africa are already using such parameters in evaluating new finds. Also Afro Asian joint efforts are noted [R1].

R1 - Lekana-Douki JB, Bhattacharya D, Zatra R, Fousseyni ST-N. Indian anti-malaria OMARIA is effective against African drug resistant *P. falciparum* field isolates and laboratory strains; without toxicity. **International Journal of Clinical Medicine**. 2012;3(1):1-8. doi:10.4236/ijcm. 2012.31001.

SECTION 2.10,

Around Line No. 653 :

****** Among the various types of in-vivo studies evaluation in infant/pediatric stage (1st time infestations in chronic/drug resistant domains – specially) is very essential and also extremely difficult. From Asia we note such a case [R1].

R1 - **Advances in infectious Diseases**. 2012; Vol. 2: pp.13-18. doi:10.4236/aid.2012.21003.

Section 2.1.1

****** Resistance is considered as control in Drug Discovery Studies. Resistance to Artimesinin is also being reported along with strange mutations of parasites [R1].

R1 - Story from BBC NEWS: <http://news.bbc.co.uk/go/pr/fr/-/2/hi/asia-pacific/8073118.stm>
Published: 2009/05/29 03:36:25 GMT

Section 2.2. Line No. 673-720

****** *There has been considerable movement about Vaccine for malaria. Some of them are articulated by WHO [R1], Some are internationally propelled being drug development oriented 'donor driven [R2] while others are academic and even critical reviews [R3 & 4]. There are also set-back stories about the efforts-future of malaria vaccine; etc. [R5].*

R1 - WHO. Malaria Vaccine Rainbow Tables. 2012.

Available. www.who.int/vaccine_research/en/Rainbow/index.html.

R2 - Malaria Vaccine Technology Roadmap Final Report, (2006).

Available. http://www.malariavaccine.org/files/Malaria_Vaccine_TRM_Final_000.pdf

R3 - L. Schwartz, G. V. Brown, B. Genton and V. S. Moorthy, "A Review of Malaria Vaccine Clinical Projects Based on the WHO Rainbow Table," *Malaria Journal*, Vol. 11, 2012, p. 11.

[doi:10.1186/1475-2875-11-11](https://doi.org/10.1186/1475-2875-11-11)

R4 - L. Veronic and P. Karanis, "Malaria Vaccine: Looking Back and Lessons Learnt," *Asian Pacific Journal of Tropical Biomedicine*, Vol. 1, No. 1, 2011, pp. 74-78. [doi:10.1016/S2221-1691\(11\)60072-5](https://doi.org/10.1016/S2221-1691(11)60072-5)

R5 - Reuters. Setback For First Malaria Vaccine In African Trial. Nov. 2012.

Available. www.reuters.com/.../us-malaria-vaccine-gsk-idUSBRE8A80I120121.

Other references if any.

NOTE : Reviewer could not locate any reference to the following :

A – use of Bed Nets

B – use of toxin impregnated bed nets. Authors may kindly look these 2 matters.

Table – 1 be re-captioned as follows :

Plants used for Anti-Malaria purposes in Central Tropical Africa : Select List