



Natural cocoa as diet-mediated antimalarial prophylaxis[☆]

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SUMMARY

Background: The Maya of Central America are credited with the first consumption of cocoa and maintaining its ancient Olmec name *kakawa* translated in English as “God Food”, in recognition of its multiple health benefits. The legend of cocoa is receiving renewed attention in recent years, on account of epidemiological and scientific studies that support its cardiovascular health benefits. Increasing numbers of scientific reports corroborating cocoa’s antiquated reputation as health food persuaded this author to promote regular consumption of cocoa in Ghana since 2004. Cocoa is readily available in Ghana; the country is the second largest producer accounting for 14% of the world’s output. Numerous anecdotal reports of reduced episodic malaria in people who daily drink natural unsweetened cocoa beverage prompted a search for scientific mechanisms that possibly account for cocoa’s antimalarial effects. This paper presents the outcome as a hypothesis.

Methods: Internet search for literature on effects of cocoa’s ingredients on malaria parasites and illness using a variety of search tools.

Results: Evidential literature suggests five mechanisms that possibly underpin cocoa’s anecdotal antimalarial effects. (i) Increased availability of antioxidants in plasma, (ii) membrane effects in general and erythrocyte membrane in particular, (iii) increased plasma levels of nitric oxide, (iv) antimalarial activity of cocoa flavanoids and their derivatives, and (v) boosted immune system mediated by components of cocoa including cocoa butter, polyphenols, magnesium, and zinc.

Conclusion: A hypothesis is formulated that cocoa offers a diet-mediated antimalarial prophylaxis; and an additional novel tool in the fight against the legendary scourge.

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Background

The concurrence is almost surrealistic, that a legendary food such as cocoa provides protection against a legendary disease such as malaria. Ironically, although the tropical regions in the world that produce cocoa closely overlap those that are malaria-endemic, possible antimalarial benefit may have escaped notice for at least two reasons. Firstly, cocoa is least consumed by the countries that produce the crop. The Cocoa Producers Alliance (COPAL) which has a membership of ten producing countries, accounts for 75% of the world’s cocoa produce but about 4% of its consumption (Secretary General of COPAL, personal communication). Secondly, processing into chocolate and other more palatable beverages which represent the predominant form in which modern cocoa is consumed decreases its antioxidant content, and perhaps removes other vital micronutrients necessary for antimalarial effect. A recent study showed that natural (unsweetened) cocoa powder being the least processed cocoa contains the highest levels of Total Antioxidant Capacity (TAC) and procyanidins; compared to Dutch processed

(alkalized) cocoa powder, unsweetened baking chocolate, semi-sweet chocolate baking chips, dark chocolate, and milk chocolate [1].

Malaria is a pre-eminent tropical parasitic disease and one of the top three killers among communicable diseases [2]. It is a public health problem in more than 90 countries inhabited by about 40% of the world’s population, with the global disease burden estimated at 1.1 million deaths per annum, of which over 90% is in sub-Saharan Africa [3]. A number of interventions are being promoted in malaria-endemic regions of the world to control, treat, and prevent malaria. However, worrying trends over the last few decades portend worsening malaria disease burden worldwide. Included in these trends are an increase in epidemic malaria; upward trends in mortality; an upward trend in drug-resistant *Plasmodium falciparum* malaria; re-emergence of *Plasmodium vivax* malaria in areas from where it has previously been eradicated; and an increase in imported malaria in the developed world [4]. According to the latter reference, a six-point Roll Back Malaria (RBM) strategy, which has been fashioned by the WHO includes: “Development of new tools, strategies and methodologies, and improvement in delivery of existing tools through research and development”. It is now reasoned that effective malaria control programmes must be fashioned using a combination of interventions adapted to local

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needs based on specific ecological, epidemiological, economic and social conditions. Against this backdrop, unsweetened beverages of natural cocoa powder as diet-mediated antimalarial prophylaxis offers a novel tool that holds unprecedented health and socio-economic prospects for many developing countries, especially those that are also cocoa producers.

The Maya of Central America are credited with the first consumption of cocoa (500 AD) and maintaining its ancient Olmec (1000 BC) name *kakawa* [5] that in English translates as “God Food”, in recognition of its multiple health benefits. The legend of cocoa as health food is receiving renewed attention in recent years, on account of epidemiological and scientific studies that support cardiovascular health benefits [6–8]. In 2006 Hollenberg [9], who for more than a decade continues to contribute immensely to the rising interest in cocoa’s health benefits, having noted the impressive list of candidate conditions that might be influenced (by cocoa flavanols) declared “The next decade will be interesting”. This optimism concerning cocoa as a health food is contemporaneously correct with possibilities such as presented in this paper for its use as a dietary antimalarial prophylaxis.

Cocoa as a health food

Whilst screening a variety of foods for their acidogenic effects on teeth in 1994, the present author serendipitously found that *Golden Tree* brand of milk chocolate produced in Ghana (containing 30% cocoa solids) was non-acidogenic [10]. Literature research for possible reasons why the chocolate was not harmful to teeth (despite its high sugar content) yielded extensive information on health benefits of cocoa. There is persuasive documented evidence that cocoa is a rich source of polyphenolic compounds, and that consumption of foods rich in polyphenols is associated with reduced risk of cardiovascular disease [6,9,11]. Polyphenols have a subgroup known as flavonoids, and a specific subclass of flavanols. Flavanols occur in monomeric forms as (–)-epicatechin and (+)-catechin, which are found in several food sources including cocoa and tea. Cocoa also contains oligomeric flavanols built from monomeric units and known as oligomeric procyanidins or OPCs [8]. These bigger flavanols (OPCs) found in cocoa are not found in such abundance in any other plant foods or beverages [12,13]. Human conditions that may be prevented by consumption of cocoa rich in flavanols include cardiovascular disease, diabetes mellitus [7,14]; dementias, strokes and end-stage renal disease [9,15,16]. Another advantage as health food is that unlike tea and coffee that are sources of caffeine, cocoa contains little caffeine (0.2% by weight). The main methylxanthine in cocoa is theobromine (2–3% by weight) which has little stimulating effect on the central nervous system. Therefore, cocoa can be given to children without fear of inducing hyperactivity or sleeplessness [17]. This is exceptionally important for the hypothesis presented in this paper because most deaths attributable to malaria occur in African children less than five years old [4].

Persuaded by cocoa’s potential to prevent age-related health problems, promote better cardiovascular and mental health, and facilitate treatment of many disease conditions; this author has been actively promoting regular cocoa consumption in Ghana since 2004. Ghana is the second leading producer of cocoa accounting for 14% of the world’s output [18]. The self-initiated “drink cocoa daily for better health” campaigns have attracted collaborative efforts from local institutions such as Ghana Science Association (GSA), Ghana Cocoa Board (COCOBOD), Cocoa Research Institute of Ghana (CRIG), and the international institution COPAL. Among many health benefits anecdotally reported as public feedback, is reduced frequency of malaria illness in people who daily drink unsweetened beverage made by mixing boiling-hot water and factory processed natural cocoa powder containing (12–15% cocoa butter).

Since becoming the unofficial foremost promoter of regular cocoa consumption in Ghana (in 2004), there has been no episode of malaria in this author’s household of four people who drink cocoa beverage 2–5 times everyday. Before daily cocoa consumption, this author personally had at least one episode of malaria each year. These anecdotal observations confirmed by many people, prompted a search for scientific mechanisms that could explain how dietary cocoa may protect against malaria illness, based on known effects of some of the dietary nutrients found in cocoa. The aim of this publication is to submit a hypothesis that explains cocoa’s antimalarial effects at the mechanistic level to wider scientific scrutiny and provoke empirical validation.

Prospects for increasing cocoa consumption in producing countries and reducing malaria prevalence

West Africa is included in those regions in the world where malaria and poverty present a commutatively synergistic scourge. According to Food and Agriculture Organization [18], by the year 2010 countries in West Africa would account for about 66% of the world’s cocoa production but less than 14% of consumption. The low consumption in producing countries means that the health benefits obtained from cocoa as food are largely unavailable to them. If the anecdotally reported antimalarial effects of cocoa are empirically confirmed, it should open a big internal consumption market in producing countries and provide economic motivation for increased grindings that could stabilize international price of the crop. Being locally available, encouraging consumption of the most healthful cocoa food (the least processed natural cocoa powder) should not present formidable problems, and governments should find the economic advantage in adding dietary cocoa to their arsenal for malaria control. The magnitude of benefit globally should greatly offset investment in research to validate anecdotal reports that regular consumption of natural cocoa powder as an unsweetened beverage coincides with reduced episodes of malaria in people of all ages.

Hypothesis

Anecdotal reports and personal subjective observation that daily intake of a beverage of cocoa powder protects against episodic malaria appears to have evidential scientific support centred on five potential mechanisms as follows: (i) increased availability of antioxidants in plasma; (ii) cell membrane effects in general and erythrocyte membrane effects in particular; (iii) increased plasma levels of nitric oxide; (iv) antimalarial activity of cocoa flavonoids and their derivatives; (v) boosted immune system mediated by components including cocoa butter, polyphenols, magnesium, zinc, copper, and chromium.

Increased availability of antioxidants in plasma

Cocoa has plentiful antioxidants [19,20] mainly on account of high polyphenol content. Plasma concentration of antioxidant flavanols have been shown to rise significantly after ingestion of cocoa products [7,21,22]. Even complex polyphenols (procyanidins) whose bioavailability was once in doubt, have been detected in human plasma following consumption of flavanol-rich cocoa [23,24]. Although there seems to be a paradoxical role of antioxidants in malaria parasitaemia, evidence exists that high plasma concentration of antioxidants coincides with less severe malaria [25] or more rapid clearance of parasitaemia [26]. Malaria parasites generate reactive oxygen species (ROS) as by-products of their metabolism. During their erythrocytic life stages, malaria parasites have a high metabolic rate associated with their rapid growth/multiplication

and generate large quantities of redox-active metabolites, which result in oxidative stress [27]. Thus, there is increased oxidative stress during malaria infection [28–30], ascribed to both the malaria parasite's metabolism [31–33] and host immune response [34–37]. Ironically, the malaria parasite is highly susceptible to oxidative stress [27,38–40]. This has led to prevalent supposition that hereditary conditions such as haemoglobinopathies (sickle cell and thalassaemias) and glucose 6 phosphate dehydrogenase deficiency (G6PD) [41,42]; as well as dietary adaptation that includes consumption of 'oxidant fuels', high intake of iron, and limitation of antioxidant intake or storage [42] confer protection against malaria infection by creating low antioxidant levels in blood. Moreover, depressed plasma concentration of antioxidants is concurrent with acute malaria in children [25,26,28,43,44], and adult patients [45,46]. Pertinently, antioxidant supplements ameliorate symptoms and decrease duration of infections including malaria [26,28,47,48], decrease malaria-associated endothelial apoptosis *in vitro* [49], and prevent cerebral malaria in mice [50].

The present postulate is that high plasma concentrations of antioxidant flavonoids obtained by regular intake of natural unsweetened cocoa beverage would permit scavenging of ROS and other free radicals produced by the malaria parasites and host response. The high plasma antioxidant concentration would also mitigate the pro-inflammatory response of the body's immune system to the parasites [51] thereby ablating the cascade of molecular events that exacerbates the pathophysiology of malaria [52,53]. For effective protection against malaria episodes, the cocoa powder beverage must be taken daily and preferably more than once every day. This is because of the relative shortness of plasma half-life of flavonoids (<24 h), as a result of which plasma epicatechin concentration typically returns to baseline values within 6–8 h after ingestion of cocoa product [24,54–56].

Cell Membrane effects

Cocoa procyanidins have been reported to protect membranes against both chemically-induced oxidation and detergent-induced membrane disruption [57,58]. In both *P. falciparum* and *P. vivax* parasitaemia, decreased serum vitamin E is thought to arise in part because of its transfer to the red cell membrane to counteract increased oxidative stress during acute phase of the disease by inhibiting membrane peroxidation [45,59]. It is presently proposed that flavonoid-mediated resistance to oxidation would augment antioxidant protection of membranes in cells exposed to malaria parasitaemia and help to keep oxidative stress under control. It is stimulating in this regard, those erythrocytes from subjects consuming flavonoid-rich cocoa show reduced susceptibility to free radical induced haemolysis [60]. The advantage of membrane stability in ameliorating malaria pathophysiology resides in the fact that erythrocytes may not be easily infected by the parasites, and when infected cells are resistant to haemolysis they will interfere with the life cycle of the parasite. Additionally, improved erythrocyte membrane resistance to haemolysis would attenuate protection of malaria parasites from serum nitric oxide and ROS offered by extracellular plasma haemoglobin [61,62]. Furthermore, flavonoid-induced resistance of erythrocytes to haemolysis would mean that plasmodium haeme products (haematin and malaria pigment) that destabilize and lyse human erythrocytes [63] would be less available in plasma to cause damage.

Increased plasma levels of nitric oxide

That ingestion of flavonoid-rich cocoa produces high plasma levels of nitric oxide (NO) has been excellently reviewed [7,8,64]. NO-related species mediate inhibition of malaria parasites by hepatocytes and monocytes [65–68]. NO has also been shown to

kill parasites *in vitro* via its derivatives known collectively as reactive nitrogen intermediates (RNI) including nitric oxide radical, its oxidized forms nitrite and nitrate [69–72]. Nahrevanian and Dascombe [73] found that production of NO during lethal and non-lethal strains of malaria was consistent with a role for protection of the animals against plasmodium. In deducing a protective rather than pathological role for NO in African children, Anstey et al. [74] found an inverse relationship between malaria severity and NO production/NO synthase type 2 (NOS2) expressions. Interestingly, the latter authors posited that high fasting plasma NO levels and leucocyte NOS2 in healthy controls and asymptomatic infection suggest that the increased NO synthesis might protect against clinical disease. This inference permits speculation that high plasma levels of NO in people who regularly drink pure unsweetened cocoa beverage contributes to anecdotal absence of symptomatic malaria.

The clinical consequences of intravascular haemolysis and its accompanied extracellular haemoglobin have been beautifully reviewed [75]. One possible protective mechanism for malaria parasites by haemolysis-produced extracellular haemoglobin is its exquisite scavenging ability for NO and dysregulated arginine metabolism, which limits bioavailability of NO and toxicity to plasmodium. As indicated above, cocoa flavonoids can confer resistance on erythrocytes to haemolysis, ensuring that little haemoglobin is extracellularly available to protect malaria parasites before they enter cells. It is also attractive to speculate that high plasma NO levels in people ingesting flavonoid-rich cocoa would ensure that there is excess NO derivatives to inhibit plasmodium that are released from any minimal haemolysis of infected cells.

Antimalarial activity of cocoa flavonoids

Diglycosides of flavanols (a specific type of flavonoids) have been shown by Murakami [76] to retard life cycle of malaria parasites, whereas monoglycosides completely inhibited proliferation of trophozoite stage of parasites. Flavonoid derivatives dehydrosilybin and 8-(1;1)-DMA-kaempferide exerted significant antimalarial activity against five strains of *P. falciparum* [77]. The latter authors suggested that flavonoid derivatives could be used as adjunct to already available antimalarial drugs to delay the spread of resistance in *P. falciparum*. More recently, when several flavonoids including the flavanols kaempferol, quercetin and isoquercetin were screened for inhibitory effects on intraerythrocytic malaria parasites, quercetin and the flavone luteolin showed the highest individual activity, whilst even less active flavonoids exhibited synergistic and additive effects at lower concentrations [78]. Remarkably, the last study showed that the flavonoids inhibited *in vitro* growth of both chloroquine-sensitive (3D7) and chloroquine-resistant (7GB) strains of *P. falciparum*. One preliminary determination of the antioxidants present in a Ghanaian cocoa powder brand that this author drinks regularly by collaborators at the University of Greenwich, U.K. indicated that the highest peak was produced by quercetin (Amuna and Zotor – personal communication). Taken together, these pieces of information clearly suggest that attenuated symptomatic malaria in people drinking pure unsweetened cocoa powder beverage, is partly a manifestation of benefits from a flavonoid diet-mediated antimalarial prophylaxis.

Boosted immune system

Although host immunity to malaria parasites is complex and yet to be fully understood, people in endemic areas subject to repeated infections frequently carry small numbers of parasites in the blood with little symptoms of the disease, illustrating a phenomenon

termed semi-immunity [79]. Meanwhile, a study on cocoa polyphenols and human cytokine activation concluded that cocoa, as a potential immune modulator, may have therapeutic advantages in human disease that involve activation of the immune system [80–82]. Additionally, cocoa contains significant levels of magnesium and copper, as well as dietary trace minerals including copper, zinc, manganese, and chromium; all of which have been credited with improving activity of the immune system [83].

Conclusion

Evidential literature supports anecdotal reports and personal experience in Ghana that daily intake of pure unsweetened cocoa powder beverage offers protection against symptomatic malaria. It is therefore hypothesized that cocoa offers food that may be deployed as a diet-mediated antimalarial prophylaxis. There is need however for properly conducted longitudinal study to validate this hypothesis and to determine the percentage points by which the cocoa-mediated antimalarial effect is obtained in selected cohort populations. In the meantime, without any known problematic effects for consumers, there is every good reason for people to patronize pure unsweetened cocoa as beverage, and other cocoa products high in flavanols and low in calories and other worrisome additives as prophylaxis against malaria parasitaemia.

The role of funding sources

The Dreyfus Health Foundation (DHF) of New York funded the initial study titled “Efficacy of stick chewing in reversing acidogenic challenge to teeth after Ghanaian meals”. They reviewed and approved the research proposal, provided funds to carry out the study, and give a public presentation of findings that included the non-acidogenic effects of *Golden Tree* milk chocolate. DHF has had no further role in subsequent research on cocoa and has no part in the decision to submit this paper for publication. No other past or potential future sponsor has a part in the decision to publish this manuscript, which has been put together at the authors own cost.

Conflict of interest statement

The Government of the Republic of Ghana through the Ghana Cocoa Board (COCOBOD) and the Cocoa Research Institute of Ghana (CRIG) sponsored and encouraged the promotion of cocoa consumption (in Ghana), and financed the author’s attendance of the 15th International Cocoa Research Conference (ICRC) in San Jose, Costa Rica, October 2006. The Cocoa Producers Alliance (COPAL) invited the author to give a lecture on “Health and Medicinal Benefits of Cocoa and Cocoa Products: the Challenges and Prospects for Cocoa Producing Countries” at the 69th General Assembly and Council of Ministers Meeting, Abidjan, Cote d’Ivoire; September 2006. The author received a Consultant’s fee for the lecture. Ghana COCOBOD, and the Cocoa Processing Company (CPC) were part-sponsors with other Ghanaian firms of the first public lecture given by the author on “The healthful Benefits of Chocolate and Cocoa Products”, September 2004. The lecture was organized under the auspices of the Ghana Science Association (GSA), which was subsequently engaged by the Ghana COCOBOD to organize a Quiz Competition in second cycle institutions in Ghana on the “Benefits of Cocoa to Ghana”. The author was engaged as a consultant to prepare an information booklet for the schools, and received payment for that service. The author is part-owner of a nascent Ghanaian Registered (2008) ultra mi-

cro-Enterprise, Kakawa Enterprise Limited, that promotes regular consumption of natural cocoa through public education, research, and product development.

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