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The Role of Kola Nut (*Cola Nitida*) in the Etiology of Malaria Morbidity

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Abstract

The contribution of kola nut in mimicking malaria-like morbidity in apparently healthy volunteers was evaluated. Thirty-five grams of *Cola nitida* was given to each of the 48 volunteers who were known not to have taken kola nut or coffee in the previous one month for three consecutive days. The blood samples of these volunteers were enumerated for malaria parasites before serving them the kola nut. The sampling of blood was repeated on the 2nd and 3rd days for the presence of malaria parasites. Blood samples were also taken from known kola nut addicts (those that eat kola nut on daily basis). It was found that 16 (33.3%) of the volunteers had malaria parasites in their blood at the inception of the study while 32 (66.7%) had no detectable parasites. Four days after, 10 (20.8%) of the volunteers that did not show detectable parasites on the first day now had parasites. Those that showed detectable parasite before taking the kola had significant increase in parasite density. Statistical analysis showed a strong relationship between parasite increase and eating of the kola nut (Chi-squared, $X^2 = 14.83$, $p > 0.0001$ at 95% confidence limit). The volunteers reported clinical symptoms of sleeplessness, lack of concentration, dizziness, and weakness observable in malaria patients. There was no association between malaria parasite presence and clinical complaints ($X^2 = 3.75$, df = 1, $p = 0.05$). It was found that 11 people without the malaria parasite in their blood before and after taking the kola nut complained of various malaria symptoms confirming that kola nut can mimic malaria-like symptoms. In conclusion, it can be said that kola nut taken at a high concentration (about 35 g/day) will mimic malaria-like symptoms. This quantity will leave a high level of caffeine and cyanide in the circulation so that people with a low level of malaria parasite in them will notice active infection which otherwise may have been controlled by the host immune system. Lastly, the observed phenomenon can affect drug pressure and induce resistance to antimalarial drugs. The mechanism of kola nut action that influences malaria-like morbidity is discussed.

Keywords: Malaria, caffeine, cyanide, morbidity, *Cola nitida*.

Introduction

Cola nitida Schott and Endl (Sterculiaceae) (Kochhar, 1986), commonly called Kola nut, is produced in different geographical areas of Nigeria. In fact, Nigeria produces 88% of the world's *Cola nitida* crop (Philips, 1977). Of this total, 90% is consumed within the country. The nuts are used in several ways, including preparation of kola and cocoa cola type beverages, as a source of alkaloids in pharmaceutical industries, and as a source of essential oil for flavoring in the confectionary industry (Philips, 1977). It has been observed that kola nut contains 3% caffeine and smaller amounts of theobromine and kolanin that dispel sleep, thirst, and hunger (Eijnattern, 1969). It also contains anti-nutrient substances such as hydrocyanic acid, which in large amounts reduce the quality of food in terms of its nutrient utilization (Chakraborty, 1976).

Malaria, on the other hand, is recognized as a public health problem and a serious obstacle to socio-economic development, especially in rural areas of malaria endemic countries. The enormous loss of lives and days of labor, the cost of patient treatment and the negative impact of the disease on development, make malaria a major global, social and economic burden (WHO, 1993). Malaria control is a global

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problem today with emphasis being placed on mortality and morbidity reduction. In Nigeria, malaria is the most commonly reported disease and is among the three main causes of death (Ekanem, 1991). Defining the factors that govern the interactions of the parasite with its host in a given area should greatly facilitate the design of effective malaria control measures (Viriyakosol, et al., 1995).

A qualitative pilot study has shown that 8% of a study population that eats kola nuts is predisposed to malaria attack while 70% of this population showed overt clinical symptoms of malaria (Kalu, 1996).

This research focuses on the possible link between consumption of kola nut and increased malaria-like morbidity in the Calabar area. The study objective is to establish whether the eating of kola nut significantly influences the expression of clinical malaria symptoms.

Materials and methods

This work was carried out in Calabar Municipality of the Cross River State of Nigeria. The study was a prospective analytic study carried out with questionnaire and experimentation. Forty-eight apparently healthy men and women volunteers (age range 18–45 years) were enrolled in the trial (the volunteers for the test were undergraduate students in the University of Calabar). Only the volunteers who had not taken immunosuppressive drugs including steroids and antimalarials in the previous 2 months were allowed to enroll. They were given a consent form to sign before being allowed to take part in the study, as well as a questionnaire to complete. The questionnaire carried details of their knowledge of malaria attack in the previous 12 months and whether or not they had eaten kola nut in the previous month. Those that had taken kola nut were not allowed to participate in the study. They were told to indicate whether they drink cocoa kola, coffee, alcoholic drinks and the type or name of drugs taken in the previous month. They were to indicate the date of last malaria attack and the drug taken for it. Attempts were made to use people without the malaria parasite in their blood on the 1st day of enrollment, but it was so difficult to recruit participants. Out of every 5 people screened one had a certain amount of the parasite even though they looked healthy and symptomless. As a result it was decided to use any candidate that met all the above criteria disregarding his or her parasite status as a selection parameter. A control group of 48 apparently healthy men and women of similar age range with the test volunteers were recruited to assess the prevalence of malaria parasite in that category of people. These were predominantly those that eat kola nut on an almost daily basis and a good number of them sell the kola nut. Paired comparison method of evaluation where the same candidate serves as the test and control was applied on the test group to eliminate confounding factors and make stratification easy. The day zero results of the test group could then be compared with the results of the control group that eat kola nut everyday.

On enrollment, 20 µl blood smears for thick and thin films (Day zero, D°) were made. Thereafter they were given kola nut weighing 35 g each. This was taken under supervision and was repeated for 3 consecutive days. On the 4th day (day 3, D^3), thick and thin films were made. The blood films were stained in 2% Giemsa for 30 min after fixing the thin film in methanol. Any asexual parasites present in the smears were enumerated. Parasite density was estimated by counting asexual parasite in relation to white blood cell count of 8000 per µl of whole blood (Shute, 1988). The participants were allowed to comment freely on the effect of the kola nut in them before discharge. Blood samples were also collected from kola nut addicts that habitually eat kola nut on a daily basis. The samples were also stained and parasite count performed on them. The idea was to compare the day zero parasite prevalence of the test group and that of the addicts. The Day Zero (D°) sample collections made before giving them kola nut served as the negative control while the blood sample collected on the court day (D^3) served as the test sample. The kola addict group was made to complete a short questionnaire on their annual malaria rate, effect of kola on them, if any, before letting them go.

Results

Out of the 48 volunteers that participated in the study, 16 (33.3%) had low parasite count (parasite count below 500 parasites per µl) before enrollment while 32 (66.7%) had no detectable parasites. Four days after the kola exposure, 10 (20.8%) of the volunteers that did not show detectable parasites in their blood on day zero now had parasite, thus increasing the number with malaria to 26 (54.2%) at the end of the trial. Those that had parasite before the trial showed significant increase in parasite density. Table 1 shows the parasite distribution among the test group. It was found that the geometric mean parasite density (GMPD) of the volunteers was 62.5 on day zero while that of the addicts was 81.3. On the fourth day (D^3) the GMPD of the volunteers was 89.7 (Table 1). It was observed that some of the parasite increases were significant while others were not. Statistical analysis showed a strong relationship between parasite increase and the eating of kola nut (Chi-squared $X^2 = 14.83$, $p > 0.0001$ at 95% confidence limit).

The kola nut addicts (chronic eaters) had malaria parasites in the blood of 29 (60.4%) of the participants. Various symptoms normally associated with malaria patients were found in the volunteers after ingesting the kola (Table 2). Twelve people complained of headache, 10 of which had malaria parasites detectable in their blood while 2 did not show any parasite at all. Sleeplessness and lack of concentration that are observed in many malaria patients were found. Of this number, 10 people with this condition had parasites detectable in their system while none was found in the other 10. Four people who complained of dizziness had the

Table 1. Parasite distribution among test group.

	Volunteers								
	Before kola			After kola			Kola addicts		
Day	No.	%	GMPD	No.	%	GMPD	No.	%	GMPD
0	16	33.3	62.5	–	–	–	29	60.4	81.3
3	–	–	–	26	54.2	89.7	–	–	–

GMPD = Geometric Mean Parasite Density.

Table 2. Number of people who demonstrated Malaria symptoms.

	Malaria infected		Malaria uninfected	
Indicator	Before kola	After kola	Before kola	After kola
Headache	–	10	–	2
Dizziness	–	4	–	3
Sleeplessness	–	10	–	10
Fever	–	6	–	1
Loss of voice	–	–	–	1
Anxiety (increased)	–	–	–	1
Weakness	–	5	–	6
Neck ache	–	1	–	–
Apparent weight loss	–	–	–	1
Increased appetite	–	2	–	–
Feeling unwell	–	–	–	2
Body heat	–	–	–	1

Table 3. Annual malaria frequency in the participants.

Annual frequency of malaria infection	Number of respondents	Number with parasite	Number without parasite
Rarely	4	2	2
1	13	4	9 (DO/D3)
2	9	5	4
3	6	4	2
4	5	3	2
5	2	2	0
6	2	1	1
7	1	0	1
9	3	3	0 (DO/D3)
10	3	3	0 (DO/D3)

parasite in their system while the other 3 did not show any parasite.

Table 3 shows the annual malaria frequency of the test group. Sixteen respondents said that they suffered from malaria not less than 4 episodes in a year. Of this number, 9 of them did not have parasite in their blood before and after taking the kola nut. In contrast, 6 people that said they suffered from malaria between 9–10 times a year were known to be carrying malaria parasites before and after taking the kola nut.

The questionnaire response revealed that the 11 participants that did not have the malaria parasite after the test as well as 6 people whose blood samples had detectable parasites had no complaint of any sort (Table 4). In contrast, 11 of the participants who had no detectable parasites in their blood complained of one thing or another. Twenty of those that had detectable malaria parasites actually complained of different malaria signs. Statistically, there was no association between parasite presence in the blood and clinical complaints reported after taking kola nut ($X^2 = 3.75$, df = 1, p = 0.05). The use of discriminate analysis shows p = 0.5 which suggest a possible risk of an increase in malaria parasite count as a result of intake of kola nut. It can therefore be inferred that the eating of kola nut can predispose the eater to malaria-like symptoms up to a certain limit.

Discussion

Kola nut is known to contain two major ingredients, caffeine (3%) and hydrocyanic acid (Eijnattern, 1969). One of the most important things to address is the presence of the malaria parasite in the samples of volunteers that did not have any detectable parasite on the 1st day (D°) prior to ingestion of kola nut, but after 4 days demonstrate detectable parasites. These volunteers had no complaints of any sort. Four days after kola intake 31 (63.6%) of 48 complained of malaria-like symptoms. Another point of interest is the rate with which the parasites increased and showed overt symptoms of active infection "4 days after taking the kola nuts". Part of the explanation to this is probably the stage of the liver schizogony at the time the kola nut was taken. A more important explanation is the influence of the biochemical action of the two agents in kola nut. This can be explained by the interaction between caffeine and cyclic-adenosine monophosphodiesterase.

Table 4. Distribution of clinical complaints among the participants.

No parasite No complaint	Parasite present No complaint	No parasite But complaint	Parasite present With complaint
11	6	11	20

Chi-square (X^2) = 3.78, df = 1, p = 0.0513
There is no association between parasite and complaints.

Cyclic-adenosine monophosphate (cAMP) is present naturally in the blood, but its concentration is regulated by the enzyme cyclic-adenosine monophosphodiesterase. *In vitro*, this enzyme cleaves cAMP regardless of temperature (Brockelman, 1982). One approach to maintaining cAMP levels is to add compounds that inhibit cAMP-phosphodiesterase activity (Brockelman, 1982). Caffeine, theophlline and disodium ethylenediamine tetraacetic acid (Na_2EDTA) are inhibitors of this enzyme activity (Beavo et al. 1971). Cyclic-AMP is known to play an active role in the conversion of asexual stages of *Plasmodium falciparum* into gametocytes (Brockelman, 1982) and is also known to contribute to the increased parasite growth in culture medium (Asahi, 1996). Ogwang et al. (1993) also established that caffeine and theobromine can stimulate gametocytes to exflagellate in suspended animation buffer pH 7.4 at room temperature. Daniel and Oleinick (1984) concluded that caffeine can produce rapid transient elevation of cyclic-AMP and a slower delayed elevation of cyclic guanine monophosphate (cGMP) and inferred that caffeine can stimulate mitosis delayed by radiation of *Plasmodium*. At an appropriate concentration caffeine could be used to enhance gametocytogenesis without exerting toxic effects on the culture (Brockleman, 1982). These observations support the hypothesis that the more kola nut is eaten, the higher the level of caffeine in the general circulation and the greater the effect on the cyclic-adenosine monophosphodiesterase, thereby releasing more cAMP in the circulation and favoring parasite multiplication. In humans, caffeine has been associated with four important physiological actions; (1) stimulation of a large group of centers in the central nervous system; (2) a diuretic effect upon the kidney; (3) a stimulating action on striated muscle; and (4) a group of effects upon the cardiovascular system.

Fatalities from 183–250 mg of caffeine/kg body weight have been reported (Aruna, 1997). Doses of caffeine up to 10 g orally have caused gastric irritation, vomiting and convulsions; complete recovery occurred in 6 h. Repeated doses of caffeine, theophylline and their salts orally, intravenously or rectally may cause restlessness, epigastric pain, headache, nausea, vomiting, fever, psychomotor agitation; tachycardia, rambling flow of thought and speech, nervousness, excitement, diuresis, hyperventilation, convulsion and respiratory failure. Caffeine at high concentration has been shown to depress smooth muscle activity in rats (Abengowe et al., 1980). *In vivo* caffeine is known to elevate arterial blood pressure in rats. This apparent blood pressure increase, if present in humans, can present clinical signs of malaria-like heaviness of the head, headache, and dizziness. Most of these signs are reminiscent of the symptoms found in malaria patients. Table 2 confirms similar symptoms from our test group.

Kola nut is known to contain 39.42 mg of hydrocyanic acid (linamarin) per kilogram and this is known to be toxic to tissues. Toxicological studies (ATSDR, 1993) have indicated that short-term exposure to high levels of cyanide can harm the nervous, respiratory and cardiovascular systems of animals. The lethal dose for humans is 1–3 mg/kg body weight. Long-term exposure to sub-lethal dose causes irritation of the eyes, loss of appetite, headaches, dizziness and damage to the nervous system and thyroid gland (Korte & Coulston, 1998). Specifically, cyanide forms a highly stable complex with cytochrome oxidease. Since cyanide is rapidly absorbed from the gastrointestinal tract it can produce death by cellular anoxia (Eramaus et al., 1980) when it complexes with the cytochrome oxidase. The phagocytic cells and macrophages of the human body may also be affected by this cellular poisoning and could weaken the body defense mechanism in favor of parasite multiplication. Reduced activity of the defense cells due to this poisoning could undermine the production of cytokines, tumor necrosis factor (TNF) and gamma interferon (γIFN), all of which are known to inhibit replication of parasites within the hepatocytes (Kauffman, 1988). The CD^4T cells responsible for blood stage immunity and CD^8T cells responsible for sporozoite immunity would no longer function effectively and the parasites would multiply in the system, possibly enhanced by the caffeine circulating in the body, and could then be detectable in the blood. This probably explains the detection of parasites in the blood of some of the participants on D^3 that showed no parasites on D°. In endemic areas, individuals are continuously exposed to infected mosquitoes and most people harbor parasites without signs of clinical disease, sometimes even at relatively high parasite densities (Farnert et al., 1997)

The actions of both caffeine and cyanide are concentration dependent, and this was vividly seen in one of the volunteers that acted outside the confines of the trial and ate in excess of 2 kola nuts. Within 24 h his parasite count increased exponentially from 639 to 16,846 and this man caught cold after 6 h of consuming the nuts. The *Plasmodium falciparum* infections in symptomatic individuals in a holoendemic area are highly complex and changes in the parasite population occur daily both in density and genotypic pattern in response to environmental factors (Farnert et al., 1997). An important factor may be the effect of caffeine on the conversion of asexual stages of *Plasmodium falciparum* into gametocytes under the influence of c-AMP. This means that people in endemic areas that eat kola nut and take food drinks containing caffeine are more likely to be gametocyte carriers, thereby increasing the potential for parasite transmission and malaria morbidity in the population, and making malaria control a greater problem.

One of the difficulties associated with achieving a reduction in the malaria incidence is that a combination of many diverse effects contribute to the maintenance of its transmission. Blanket approaches to delivery of high technology malaria control methods are wasteful and in response a re-examination of the principles of transmission on a microepidemiologic scale to identify risk factors (Gunawardena et al., 1998) is needed.

The risk of malaria in endemic areas is probably associated with the type of food taken. This work therefore supports the hypothesis that eating of kola nut enhances *Plasmodium* survival and transmission in endemic areas.

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