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Plenary Lecture

The co-evolution of people, plants, and parasites: biological and cultural adaptations to malaria*

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The urgency generated by drug-resistant strains of malaria has accelerated anti-malarial drug research over the last two decades. While synthetic pharmaceutical agents continue to dominate research, attention increasingly has been directed to natural products. The present paper explores the larger context in which plant use occurs and considers how the selection of medicinal plants has evolved over millennia as part of the larger human effort to mediate illness. First attention is directed to indigenous medicinal plants whose anti-malarial activity is based on an oxidant mode of action, by which intracellular constituents lose electrons (become more electropositive). Next, parallels are drawn between these plant substances and a suite of malaria-protective genetic traits: glucose-6-phosphate dehydrogenase deficiency; haemoglobins S, C and E; α- and β-thalassemias. These erythrocyte anomalies are classic examples of Darwinian evolution, occurring in high frequency in populations who have experienced considerable selective pressure from malaria. Characterized by discrete loci and pathophysiologies, they are united through the phenomenon of increased erythrocyte oxidation. In this model, then, oxidant anti-malarial plants are culturally constructed analogues, and molecular mimics, of these genetic adaptations. To further reinforce the scheme, it is noted that the anti-malarial action of pharmaceutical agents such as chloroquine and mefloquine duplicates both the genetic anomalies and the folk therapeutic models based in oxidant plants. This discussion coheres around a theoretical foundation that relates plant secondary metabolites (oxidants) to plasmodial biochemistry and human biological and cultural adaptations to malaria. Co-evolution provides a theoretical link that illuminates how medical cultures manage the relationships among humans, plants, herbivores and their respective pathogens.

Malaria: Co-evolution: Oxidation: Erythrocyte disorders: Medicinal plants

Malaria in human populations

Malaria infection has strained the biological (immuno-protective) and cultural (medicinal) resources of human populations since antiquity, and is today still one of the world's most devastating diseases. Anopheline mosquitoes are the obligate intermediary host and vector of malaria parasites, species of the sporozoan genus Plasmodium. The four human-specific species are *P. vivax, P. ovale, P. malariae*, and *P. falciparum*. The origins of human malaria are traced to infections of other vertebrate, and later non-human primate, hosts hundreds of thousands (perhaps millions) of years ago. Of the more than 100 plasmodia species that infect vertebrates, only a few of the simian parasites can also infect humans. This marked host specificity confirms that the association between humans and malaria is of long duration, long enough to suggest considerable pressure for both biological and cultural adaptations. The advent of agriculture during the Neolithic period (8000–5000 BCE) was critical in establishing malaria infection in human populations. Animal and plant domestications fostered the increased population size and density that

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.
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could support 'crowd infections' such as malaria. Furthermore, agriculture was assisted by forest clearing and related environmental modifications that both encouraged mosquito breeding and destroyed the habitats of non-human primates who formerly served as the anopheline feeding targets and plasmodium hosts. The increasingly transformed environments of the modern era continue to support malaria at a very high rate of transmissibility.

Malaria life cycle and transmission

The complex plasmodial life cycle begins with gametocytes that are ingested as part of the female mosquito's blood meal, and that initiate sexual reproduction in the mosquito's stomach. The motile zygote (ookinete) migrates through and encysts to the outer surface of the stomach wall (as an oocyst). Asexual division (sporogony) within this oocyst produces large numbers of sporozoites, which migrate to the salivary glands, and from there are injected into a vertebrate host when the mosquito takes another blood meal.

In the vertebrate host asexual reproduction (schizogony) occurs first in the liver, the asymptomatic phase, and later in circulating erythrocytes. Each sporozoite invades a single hepatic cell and produces thousands of merozoites that burst out of the liver cell and invade erythrocytes. The intra-erythrocytic trophozoite (the 'ring' stage) reproduces to form a multinucleated schizont, which contains a species-determined number of merozoites. When the schizont matures, the erythrocyte ruptures and releases merozoites that infect new erythrocytes. Completing the cycle, the sexual gametocytes that develop from some of the trophozoites are infective to the mosquito.

Pathophysiology of malaria

The characteristic periodic fevers that are the signature of malaria are precipitated by synchronous parasite development and erythrocyte rupture, which releases new merozoites, malaria antigens and toxic metabolites. *P. vivax* and *P. ovale* are relatively benign infections that present with 48 h (tertian) periodicity. *P. malariae*, also benign, has a 72 h (quartan) periodicity. *P. falciparum*, malignant tertian malaria, evinces the most severe symptoms and highest mortality, and is the principal target of anti-malarial drug research. (Quotidian malaria with 24 h periodicity is usually a double tertian infection by two distinct groups of *P. vivax* or two generations of *P. falciparum*, or a mixed *P. vivax* and *P. falciparum* infection.) Early signs of malaria are fever and chills accompanied by tachycardia (rapid bounding pulse), nausea, vomiting, frequent urination and 'flu-like' symptoms. Interfebrile episodes are characterized by leucopaenia and thrombocytopaenia (abnormally low numbers of leucocytes and platelets). Later developments include haemolytic anaemia and kidney and other organ dysfunction, including hepatosplenomegaly and jaundice. In the terminal stages, *P. falciparum* becomes 'cerebral malaria' and 'blackwater fever' (haemoglobinuria). Where malaria is endemic, children younger than 5 years bear the burden of morbidity and mortality, while older children and adults may develop an 'immunity tolerance', a protection against super-infection (Taylor-Robinson, 2002).

Malaria epidemiology and anti-malarial drugs

Today, malaria is virulently resurgent, with increased severity and epidemicity. The number of malaria deaths and geographic distribution are more extensive than three decades ago. More than half the world's population lives in malaria-endemic areas, where each year an estimated two billion are exposed, 500 million cases occur and infection results in more than two million deaths (Hoffman *et al*. 2002; Warhurst, 2002). What was heralded as the 'imminent arrival' of a malaria vaccine 20 years ago still has not materialized (Rabinovich, 2002). Existing anti-malarial drugs are less effective, and insecticide resistance among anopheline vectors is a growing problem. Consequently, the options are fewer, and more expensive. Once optimistic, the WHO has in the last 10 years downgraded its objectives and shifted its rhetoric from 'eradication' to 'control' (Najera, 2001).

Natural products and malaria therapy

The urgency generated by plasmodial resistance to a growing number of pharmaceutical agents has accelerated malaria drug research over the last two decades, with a substantial amount of that effort devoted to natural products. A MEDLINE search for articles published during just the last 5 years located several hundred dealing specifically with anti-plasmodial plants. (Research on insecticides based on natural products, an important corollary to this work, is not addressed in the present paper.) These publications range across studies of single species, groups of plants from indigenous pharmacopoeias, isolated constituents, reversal of drug-resistance and influence on anti-malarial pharmaceutical agents. These articles published in the last 12 months are representative:

1. single species: crude extracts of *Uvaria klaineana* Engler and Diel (Annonaceae) are active against chloroquine-resistant *P. falciparum* (Akendengue *et al*. 2002); extracts of *Solanum nudum* Dunal (Solanaceae) have anti-falciparum activity (Pabon *et al*. 2002);
2. indigenous anti-pyretics: thirteen species from the islands of São Tomé and Príncipe (Gulf of Guinea, off the west coast of Africa) show strong *in vitro* anti-falciparum activity, including against both hepatic and erythrocyte forms, and several species are effective *in vivo* against murine *P. berghei* (do Ceu de Madureira *et al*. 2002); various combinations of these Mali plant substances act synergistically against malaria: *Mitragyna inermis* (Willd.) *O. Kuntze* (Rubiaceae), *Nauclea latifolia* (Sm.) (Rubiaceae), *Guiera senegalensis* (Gmel.) (Combretaceae) and *Feretia apodanthera* (Del.) (Rubiaceae; Azas *et al*. 2002);
3. constituents: the alkaloids febrifugine-1 and isofebrifugine-2 from the root of *Dichroa febrifuga* Lour. have strong activity against *P. falciparum* (Kikuchi *et al*. 2002); dioncophylline E, the novel naphthylisoquinoline alkaloid from *Dioncophyllum thollonii* (Dioncophyllaceae), is active against chloroquine-sensitive and -resistant *P. falciparum* (Bringmann *et al*. 2002);
4. reversal of drug-resistance: the monoindole alkaloids isoretuline and icajine from *Strychnos* spp. (Loganiaceae)

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reverse chloroquine resistance (Frederich *et al*. 2001); artemisinin from *Artemisia annua* L. (Asteraceae) reverses chloroquine resistance (Pradines *et al*. 2001);

5. influence on anti-malarial pharmaceutical agents: the monoindole alkaloid icajine from *Strychnos* spp. acts synergistically with mefloquine (Frederich *et al*. 2001); artemisinin from *A. annua* acts synergistically both with anti-malarial pharmaceutical agents (e.g. mefloquine) and with other plant-derived anti-malarial substances (e.g. quinine from *Cinchona* spp. (Rubiaceae); Gupta *et al*. 2002; Nosten & Brasseur, 2002).

Although many of these studies are based on plants identified in indigenous pharmacopoeias, they provide only minimal ethnographic depth. Typically, the findings are presented as decontextualized catalogues of plants and lists of phytoconstituents. This information provides valuable baseline data, but disappoints from the standpoints of both practice and theory. Few of these studies offer insights into the experience of real people in specific cultural and eco-political settings; and none projects the findings against some higher level of abstraction.

To fill some of those gaps, the present paper draws attention to the larger context in which plant use occurs. Specifically, emphasis is given to how the use of plants in more than one application (principally as medicines and foods), and in particular ways (in combinations, in particular doses and sequences), can affect human health. Further, consideration is given to how the selection of medicinal plants has evolved over millennia as part of the larger human effort to mediate illness. The objective is to present co-evolution as a theoretical link to illuminate how medical cultures manage the relationships among humans, plants, herbivores and their respective pathogens. A theory-driven integrated research programme should take the place of 'hit-and-miss' strategies for identifying new drugs. This issue is approached by introducing the anti-malarial plant *Artemisia annua*, in many ways a quintessential indigenous medicine: its history as a Chinese fever medicine is thousands of years old; its active principle and its derivatives produce the most rapid parasitological and clinical responses; it has the broadest stage specificity; it is non-toxic and active by all routes of administration; it potentiates pharmaceutical agents such as chloroquine and mefloquine; it is effective against multi-drug-resistant strains of malaria (Li & Wu, 1998; Balint, 2001; Christen & Veuthey, 2001; Gupta *et al*. 2002).

The chemical basis of anti-malarial action

Artemisia annua *and oxidation*

My specific interest in *A. annua* lies in what has been called its unique mode of action, oxidation (for example, see Price, 2000). It will be argued that oxidation is not a novel bioactivity, and that mode of action will be put forward as the framework for the theoretical co-evolutionary model. The active constituent in this plant is artemisinin, a compound distinguished by a dioxygen (endoperoxide) bridge that connects two parts of the C skeleton. Biochemically, then, artemisinin is an 'oxidant'. It kills plasmodia by shifting the intracellular redox balance to a more electropositive mode. Redox refers to linked reduction and oxidation reactions in which reducing agents are H donors and oxidants are H acceptors.

The importance of oxidation for malaria is that erythrocytes depend on suppression of chemical equilibrium with O_2 at the same time that O_2 transport is their principal function. Increased, and not compensated, oxidation eventuates in cell damage, which releases immature parasite forms that cannot transfer the infection to new erythrocytes. Intra-erythrocytic oxidation may increase as a consequence of ordinary metabolic fluctuations, genetic anomalies and some foods and drugs. Oxidation also is increased by certain pathologies, including plasmodial infection. This situation is apparent in malaria-infected erythrocytes that contain up to five times the normal concentration of methaemoglobin, an oxidized form of haemoglobin. Additional evidence for oxidation during malaria infection includes elevated levels of the coenzymes NAD and NADP, and glutathione (oxidized form) relative to their reduced counterparts (NADH, reduced glutathione). Other signs of oxidation are lipid peroxidation, spontaneous generation of oxygen radical species and parasite appropriation of host superoxide dismutase. These indicators reflect intra-erythrocytic oxidation of parasite origin and erythrocyte response, as well as activation of leucocyte defence (Etkin, 1997; Scott & Eaton, 1997; Schwartz *et al*. 1999; Kemp *et al*. 2002).

The oxidant action of artemisinin accelerates oxidative erythrocyte senescence and premature destruction, and release of immature parasites. Oxidation also affects the parasite directly through damage to membranes surrounding the nucleus, food vacuole, mitochondria and endoplasmic reticulum (Dhingra *et al*. 2000). The oxidizing effect of artemisinin finds analogues in pharmaceutical anti-malarial agents (e.g. primaquine, dapsone, divicine, alloxan, menadione) whose action is mediated by activated oxygen species such as H_2O_2, hydroxyl and superoxide radicals, and singlet oxygen.

Other oxidizing plants

The mode of action of several other plants with demonstrated anti-malarial activity is also attributed to constituents that promote erythrocyte oxidation. This partial list illustrates the botanical and ecological diversity of species that share this particular biochemical profile (Etkin, 1997): *Cyperus rotundus* L. (Cyperaceae), mixed auto-oxidation products of β-selinene; *Chenopodium ambrosioides* L. (Chenopodiaceae), ascaridole which is an endoperoxide; *Gossypium* spp. (Malvaceae), gossypol; *Bidens pilosa* L. (Asteraceae), phenyl-hepatrine; *Hypericum japonicum* (Guttiferae), japonicine A.

Research on northern Nigerian anti-malarial plant medicines and food species suggests that the efficacy of those plants in the prevention and treatment of malaria is attributed at least in part to oxidant action. Extracts of these species are particularly compelling (Etkin & Ross, 1997): *Acacia nilotica* Del. (Fabaceae); *Azadirachta indica* A. Juss (Meliaceae); *Cassia occidentalis* L. (Fabaceae); *C. tora* L. (Fabaceae); *Guiera senegalensis* JF Gmel (Combretaceae).

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Oxidants have been identified and chemically characterized in other plants, e.g. *Allium cepa* L. (Liliaceae), *Cinnamomum verum* J. Presl. (Lauraceae), *Myristica fragrans* Houtt. (Myristicaceae), *Ocimum basilicum* (Lamiaceae), *Syzygium aromaticum* Merr. & Perry (Myrtaceae). Although anti-malarial activity has not been reported for these species, they all play a prominent role in the medicines and cuisines of diverse human cultures. No doubt other oxidant plant substances can be identified as well, and all fit the comprehensive model developed herein for oxidant anti-malarial substances.

Drug–food synergy

Populations are exposed to plant substances not only in medicine, but also in other contexts, most prominently in the diet. There is great potential for both synergy and antagonism in the interactions among drugs and foods. Vitamins A and E, which occur widely in nature, are powerful antioxidants. In that way they antagonize oxidant anti-malarial drugs and contribute to higher parasite counts in malaria infection. Conversely, deficiencies of vitamins A and E protect against fulminant infection. Riboflavin and Se deficiencies also contribute to oxidation and suppress human and animal malarias. As transition metals, Fe and Cu can mediate the production of free radicals; foods high in those nutrients are potential oxidants with anti-plasmodial effects. Dietary Fe over-sufficiency is a proposed adaptation in some malaria-endemic areas, where high intake is linked to cultural practices such as fermenting beer in iron containers. Total body stores of Fe and Cu can be further affected by Zn, which itself is redox inactive, but it competes with Fe and Cu for binding sites and, thus, diminishes the risk of oxidant stress. The potential effects of Fe, Zn and other divalent cations are further mediated by phytates, tannins and other chelating agents that occur as ordinary constituents in foods, medicines and other non-food items (Levander & Ager, 1993; Greene, 1997; Adelekan & Thurnham, 1998; Akompong *et al*. 2000; Shankar, 2000).

The oxidant plants mentioned earlier include clove, nutmeg, cinnamon, basil and onion. As these aromatics are both common fever medicines in indigenous pharmacopoeias and important flavour principles, anti-malarial effects can be anticipated. The view that they are 'merely' spices reflects a Western bias and may overlook the deliberate addition of these flavourings for their medicinal qualities.

Research on Hausa plants in northern Nigeria revealed substantial overlap and suggests that the seasonally-patterned use of oxidant plants in both food and medicine protects against fulminant malaria infection. Specifically, most of the Hausa plants that demonstrate oxidant and anti-malarial activities are prominent in the diet during the highest malaria risk period (Etkin & Ross, 1997). Building on this principle, other researchers have recently begun to explore nutrient-based interventions as low-cost adjuncts to current methods of malaria prevention and treatment (Levander & Ager, 1993; Shankar, 2000).

Comprehensive co-evolutionary perspectives

Discussion up to this point has established that plants offer substantial promise for the development of new anti-malarial substances, and that oxidation provides a cogent unifying principle for identifying candidate new drugs. Oxidation also provides focus for understanding how other uses of the same plants expand exposure to biodynamic activities. Food plants are especially important as they tend to be consumed in larger volume and regularly. Other plant uses (cosmetics, hygiene, dyes and craft manufacture) also afford contact with constituents that have pharmaco-dynamic potential.

From a human-centered, or even animal-centered, perspective, it might seem paradoxical that plants generate oxidants. After all, oxidants are detrimental to most life forms. It might also seem curious that taxonomically-diverse plants share this chemical signature. However, in a broad co-evolutionary model we can understand the production of these metabolites as protective; e.g. some oxidants act as toxins and anti-feeding agents to discourage insects and herbivores, others are anti-microbial and protect against plant pathogens and other oxidant compounds are allelo-chemicals that suppress the growth of competing plants (Howe & Westley, 1988; Harborne, 1993). In these ways the anti-malarial action of oxidant plants is an artifact of broad-spectrum botanical defence systems. (These relationships are not unidirectional or otherwise simple, most are multitrophic (Dicke 2000). While one species produces anti-feeding agents and allelo-chemicals, other plants and animals evolve mechanisms of chemo-detection, neutralization and detoxification. Still other organisms have saved themselves the energy required to maintain elaborate chemo-defences by evolving the visual or other organoleptic appearance of the defensive species.)

In the larger scheme it makes sense that humans have learned to take advantage of such chemo-defensive phenomena for their own purposes. The conventional view of agriculture is that the domestication of plants focused not only on greater yield and ease of harvesting, but also on palatability and diminished toxicity, so that contemporary food cultivars are mere chemical shadows of their wild counterparts. Recent research illustrates that this is not the case, even the most common foods have great potential to influence health beyond the standard nutrient measures of vitamins, protein etc. (for example, see Johns, 1996; Prendergast *et al*. 1998; Wildman, 2000).

Anti-plasmodial oxidant genotypes

Discussions of the pharmaco-dynamics of drug and food plants typically ignore human biological variability, resonating a biomedical paradigm that projects a generic human biology. Stepping outside that template, the model will be expanded once more by noting that elevated erythrocyte oxidation not only explains how some anti-malarial plants, foods and pharmaceutical agents 'work', but also the adaptive importance of several malaria-protective genotypes. These erythrocyte anomalies are classic examples of Darwinian evolution, occurring in high frequency in

populations who have experienced considerable selective pressure from malaria. While the distribution of these polymorphisms is familiar terrain in anthropology and human genetics, their shared mode of anti-malarial action is not widely appreciated. The following discussion juxtaposes these inherited aspects of malaria protection to the human management of oxidant plants.

Glucose-6-phosphate dehydrogenase deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is biochemically the best characterized of the malaria-protective genotypes. It is inherited as an X-linked recessive gene (tens of alleles are known and are characterized by similar phenotypes that vary primarily in the extent to which enzyme activity is diminished). As G6PD is the first, thus rate-limiting, enzyme of the pentose phosphate pathway, low enzyme activity results in cells that cannot adequately respond to oxidant stress. In the presence of malaria infection the integrity of G6PD-deficient erythrocytes is compromised and parasite development is interrupted. Drug-induced erythrocyte destruction in the more severe G6PD variants was linked first to anti-malarial agents such as primaquine, and has since been expanded to embrace oxidant-generating drugs generally. Medicinal and food plants also have been implicated in oxidant erythrocyte destruction and the anaemia that accompanies it (Greene & Danubio, 1997; Ruwende & Hill, 1998).

Where G6PD is relatively common, this association between consumption of certain plants and anaemia has been assimilated into local explanatory models. This knowledge allows us to pose interesting questions regarding the cultural construction of G6PD deficiency, malaria and its treatment. For example, since the earliest recorded history Mediterranean variants of G6PD deficiency have been linked to 'favism', a severe haemolytic reaction to oxidants in fava beans (*Vicia fava* L., Fabaceae). In some populations food taboos prohibit G6PD-deficient individuals from eating fava beans because of their association with anaemia. Similarly, for high-risk groups like children, fava beans are prepared by removing the seed coat, which contains the highest concentration of oxidants. Fava beans are also used medicinally; the malaria-protective effects of G6PD deficiency can be potentiated by fava consumption, and for G6PD-normal individuals the cultivation of fava beans is deliberately configured so that consumption coincides with periods of peak malaria risk. In this way both enzyme-deficient and enzyme-normal individuals are afforded protection through increased erythrocyte oxidation due to ingestion of fava beans. Oxidant plants recognized in other cultures where G6PD deficiencies occur are also subject to customs that govern who can or cannot use that species, how it should be harvested and prepared, and the timing of consumption. In another cultural spin some Chinese populations divide medicinal plants into cold or yin oxidant species and hot or yang antioxidants (Lin *et al*. 1995). In both the Mediterranean and Chinese examples cultural dicta have a bearing on the biophysiology of both G6PD deficiency and the various plants that interact with it.

Haemoglobinopathies and other inherited protections

Several haemoglobin disorders also occur as malaria-protective balanced polymorphisms. Haemoglobins S (sickle cell), C and E are inherited as autosomal recessive structural abnormalities, each allele coding for a single amino acid substitution in the β chain of the haemoglobin protein. The α- and β-thalassemias are also autosomal recessive traits, the result of underproduction of either α or β haemoglobin chains respectively. In each case, like G6PD deficiency, the selective advantage lies with the heterozygous individual who is protected against fulminant malaria infection and has no, or fewer, clinical signs associated with the disorder. The anti-malarial effects of these erythrocyte anomalies also are explained by elevated intra-erythrocytic oxidation in infected cells, evidenced by high concentrations of methaemoglobin, NAD, NADP and the oxidized form of glutathione relative to their reduced counterparts (haemoglobin, NADH, NADH and reduced glutathione), lipid peroxidation and the presence of oxygen radical species. As in the case of G6PD deficiency, increased oxidation interferes with parasite development and survival, accelerates infected erythrocyte clearance by phagocytosis and may impede parasite entry into the erythrocyte (Chan *et al*. 1999; Destro-Bisol *et al*. 1999; Tesoriere *et al*. 2001).

Conclusion: co-evolution, genetic and cultural adaptations

The erythrocyte abnormalities discussed earlier represent the most expensive mode of adaptation, in which protection is conferred on a particular genotype. Conversely, the cultural management of medicines and foods is less expensive in the sense that it is not genetically 'hard-wired', but changeable and reversible within one lifetime. Culture affords us considerably more flexibility in achieving therapeutic and preventive objectives. In the case of managing oxidant medicines and foods, human cultures have refined the biological templates represented by G6PD deficiency and the malaria-protective haemoglobinopathies. In eventually developing pharmaceutical agents such as primaquine, humans duplicated the folk therapeutic models based in oxidant plants, which are themselves molecular mimics of the genetic adaptations.

In the scientific literature oxidation is typically portrayed as detrimental; for example, its roles in carcinogenesis and cardiovascular disease are emphasized. This knowledge has been transposed in abbreviated form to the lay public, many of whom know they want antioxidants, although they are not sure why. Various lines of inquiry that converge to demonstrate the benefit of oxidation in malaria prevention and therapy have been presented. The characterization of oxidants, their basis in the chemical defences of plants and their interaction with malaria offers insights into the complexity of malaria prevention and cure.

This discussion offers a theoretical perspective for understanding how medical cultures mediate the intersection of co-evolutionary modes that involve humans, plants, herbivores and all their respective pathogens. Ultimately, this perception allows us to appreciate that

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human adaptation to malaria is complex and profoundly biocultural. On the practical side this insight suggests a paradigmatic shift in the way that plants can be evaluated for anti-malarial potential. On a more abstract level, following the theme of oxidation, we see continuity in the face of a shifting dynamic of biology and culture, stretching back as far as the Neolithic period.

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