Self-Medicative Behavior in the African Great Apes: An Evolutionary Perspective into the Origins of Human Traditional Medicine

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Close to a century ago a Tanzanian medicine man, Babu Kalunde, discovered an important treatment that saved the lives of many people in his village, who were suffering an epidemic of a dysentery-like illness. He learned about the potential medicinal value of a plant known to the WaTongwe as *mulengelele* by observing a similarly sick young porcupine ingest the roots of the plant. Before these opportune observations, Babu Kalunde and the people of his village had avoided this plant, which they knew to be highly poisonous. After telling the villagers his story of the porcupine, however—and taking small doses of the plant himself—he persuaded them to use the plant on the sick. To this day, the WaTongwe use the roots of mulengelele as medicine. Babu's grandson, Mohamedi Seifu Kalunde, now a respected elder and healer himself, uses this plant to also treat gonorrhea and syphilis.

By comparison with Babu, scientists are latecomers to the study of animal self-medication and its possible applications for modern medicine. In recent years, however, a growing body of scientific evidence has been gathered in support of animal self-medication, or zoopharmacognosy (Huffman 1997). Starting with chance observations of a sick chimpanzee in 1987 (Huffman and Seifu 1989), Mohamedi and I have worked together with a growing group of collaborators to learn how chimpanzees in the wild deal with parasites and what their behavior can tell us about treating other diseases.

Unnecessary for nutrition, growth, or reproduction, the secondary compounds in a plant have evolved to give protection from insect and mammalian predators. Whereas ecologists who study animal foraging behavior focus on how animals cope with these secondary compounds in their diet (Freeland and Janzen 1974, Glander 1975, 1982, Hladik 1977, Janzen 1978, Wrangham and Waterman 1981), the basic premise of zoopharmacognosy is that animals utilize these secondary compounds to medicate themselves. Taking a broader perspective, we are interested in putting these lessons of evolutionary medicine to practical use for humans (Huffman and Seifu 1989, Ohigashi et al. 1994, Plotkin 2000).

IN ADDITION TO GIVING US A DEEPER UNDERSTANDING OF OUR CLOSEST LIVING RELATIVES, THE STUDY OF GREAT APE SELF-MEDICATION PROVIDES A WINDOW INTO THE ORIGINS OF HERBAL MEDICINE USE BY HUMANS AND PROMISES TO PROVIDE NEW INSIGHTS INTO WAYS OF TREATING PARASITE INFECTIONS AND OTHER SERIOUS DISEASES

Much of the plant material that is consumed by animals in the wild contains an array of secondary compounds. Johns (1990) argues that the herbal medicines and modern pharmaceuticals used by humans today have replaced the nonnutritive chemicals commonly present in our primate ancestors' diets. In this light, the nonnutritive components of items ingested by African great apes—and, indeed, all

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primates—are worth investigating in greater detail for clues to the medicinal advantages that such a diet may afford.

In traditional human societies, the difference between food and medicine may not always be clear. This idea is expressed in a Japanese saying, "ishoku dougen," which directly translated means "medicine and food are of the same origin." It is perhaps no coincidence, then, that traditional spices, condiments, and vegetables used around the world are also important sources of antitumor agents or possess antioxidant, antibacterial, antiviral, and antiparasitic qualities (Ohigashi et al. 1992, Billing and Sherman 1998, Murakami et al. 1994, 1996, Sherman and Billing 1999). The concept of food as medicine goes a step further. Etkin (1996) found that 30% of the plant species identified as food among the agricultural Hausa of Nigeria were also used as medicine. Furthermore, 89% of species used to treat symptoms of malaria were also used in a dietary context (Etkin and Ross 1983). Etkin and Ross (1994) propose that many Hausa foods were originally acquired from noncultivated plants first used as medicine.

One of the difficulties of interpreting animal self-medication is distinguishing between (a) possible indirect medicinal benefits derived from secondary compound-rich plants ingested, presumably, for their nutritional value and (b) limited, situation-specific ingestion of items that are processed solely for their medicinal properties. Observations of the great apes provide the clearest scientific evidence to date for direct forms of self-medication in animals. The hypothesis I am currently developing is that these behaviors aid in the control of intestinal nematodes and tapeworms or provide relief from related gastrointestinal upset, or both. Perhaps because of their phylogenetic closeness and common neural pathways of chemosensory perception, humans and chimpanzees, when displaying similar symptoms of illness, learn to associate and select for similar properties in medicinal plants (Huffman et al. 1996a).

Unquestionably, the evolution of medicinal habits from the great apes to early hominids and modern humans has important implications for modern medicine. Thus, this article reviews the evidence for self-medication as a form of parasite control in the African great apes, relates that information to the evolution of medicinal plant use in traditional human societies, and suggests how natural plant products might play a role in modern health care.

Great ape self-medicative behavior and parasite infection

Most of the details about two types of self-medicative behavior in the great apes—namely, bitter-pith chewing and leaf swallowing—come from three study sites, Mahale and Gombe in Tanzania and Kibale in Uganda), although these behaviors have been documented from 10 additional sites across Africa (Figure 1). The geographical, ecological, and climatic variation of these sites is great, ranging from low-elevation, moist tropical forest and woodland to montane forest. Such wide variation in geography, ecology, and climate where leaf swallowing and bitter-pith chewing are known to occur suggests that great ape populations elsewhere on the continent might also engage in these behaviors.

Parasites can cause a variety of diseases that have an impact on the overall behavior and reproductive fitness of an individual. The effect of parasitosis on the host and the host's response to infection are undoubtedly the product of a long evolutionary process (Anderson and May 1982, Futuyma and Slatkin 1983, Barnard and Behnke 1990). It would be extremely surprising, therefore, if all animals had not evolved at least one means of defense against parasites.

A longitudinal investigation showed that Mahale chimpanzees (Huffman et al. 1997) are naturally infected by numerous parasite species. The species found were three nematodes, *Strongyloides fuelleborni* (thread worm), *Trichuris trichiura* (whip worm), and *Oesophagostomum stephanostomum* (nodular worm); one trematode, *Dicrocelium lanceatum* (lancet fluke); three protozoan, *Entamoeba coli*, *Endolimax nana*, and *Iodamoeba buetschlii* (all of which are amoebas); and one flagellate, *Giardia lamblia*.

Oesophagostomum stephanostomum infections were associated significantly more frequently with bitter-pith chewing and leaf swallowing (in 14 out of 15 cases, or 93%) than any of the other parasite species (Huffman et al. 1997). The evidence from Mahale points to this parasite as the stimulus for, and the only parasite directly affected by, self-medication. The nematode parasites of the genus *Oesophagostomum* (Strongyloidea, Oesphagostominae)—called nodular worms, because they encapsulate themselves in nodules in the intestinal wall during their development—are common parasites in the proximal hindgut of rodents, pigs, ruminants, nonhuman primates, and humans (Figure 2). Several species are found in gorillas and chimpanzees and occasionally in humans (Brack 1987, Polderman and Blotkamp 1995). Some of these nodular worm species are significant pathogens in domestic livestock and in primates. Symptoms of moderate to heavy infections of *O. stephanostomum*, *O. bifurcum*, and *O. aculeatum* found in apes range from anorexia, weight loss, enteritis, diarrhea, anemia, and lethargy to intense pain that simulates appendicitis. The direct economic loss caused by *Oesophagostomum* species in animal husbandry and the hazards it presents to human health have stimulated much research on their biology and control (Roepstorff et al. 1987, Polderman and Blotkamp 1995, Varady et al. 1996).

The behavioral ecology of bitter-pith chewing

Detailed plant chemistry, behavioral observations, and parasitological surveys of patently ill chimpanzees at Mahale led to the hypothesis that bitter-pith chewing has medicinal value (Huffman and Seifu 1989, Huffman et al. 1993, 1997). Very much a collaboration of scientific method and traditional knowledge, these were the first reported observations to verify illness and obvious improvements in health after chimpanzees ingested *Vernonia amygdalina* Del. (Compositae), a putative medicinal plant.

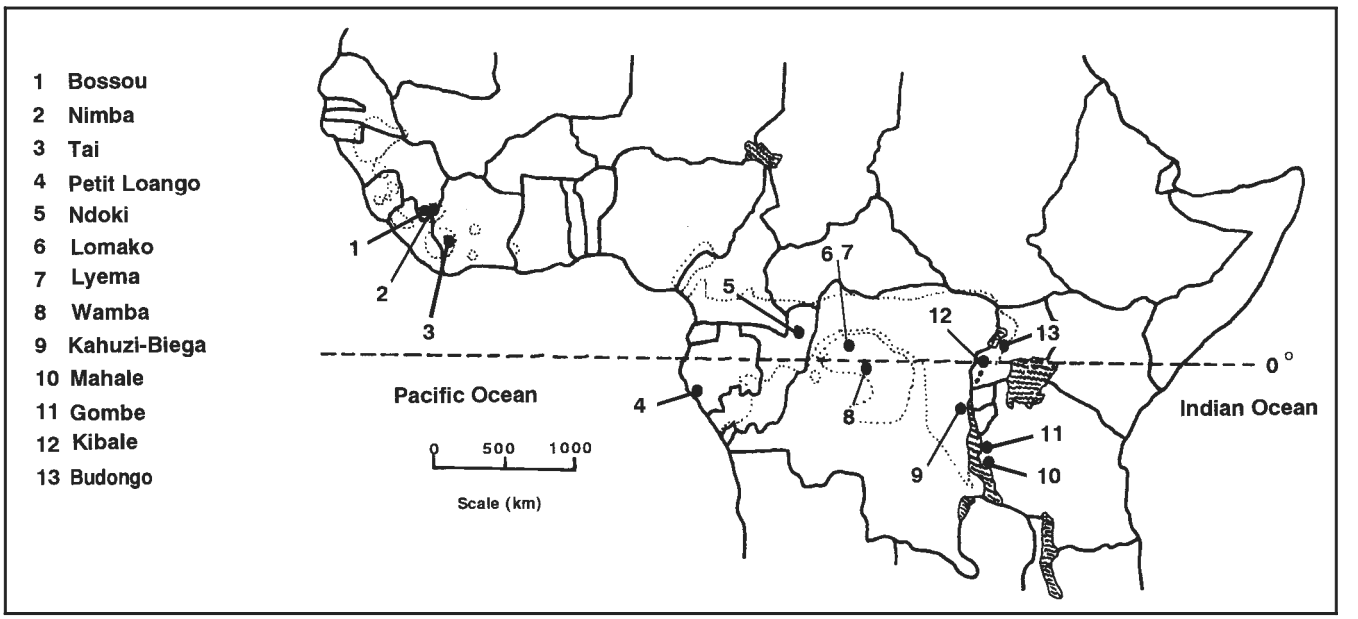

Figure 1. African great ape study sites where leaf swallowing and bitter-pith chewing behavior has been reported. The dotted areas show the current overall distribution of the African great apes: chimpanzee* (Pan troglodytes verus, *sites 1, 2, 3;* P. t. troglodytes, *sites 4, 5;* P. t. schweinfurthi, *sites 9, 10, 11, 12, 13); bonobo* (P. paniscus, *sites 6, 7, 8); and lowland gorilla* (Gorilla gorilla graueri, *site 9). From Huffman (1997), with the addition of new data from sites 4, 6, and 7 provided by Y. Takenoshita, J. Dupain, B. Fruth, and G. Hohmann.

Vernonia amygdalina occurs throughout tropical sub-Saharan Africa (Watt and Breyer-Brandwijk 1962). Chewing of the pith of other *Vernonia* species has been observed at Gombe (*V. colorata* [Willde.] Drake [Huffman and Wrangham 1994]), Hilali (Janette Wallis [Department of Psychiatry & Behavioral Sciences, University of Oklahoma Health Sciences Center], personal communication, 1999), and Kahuzi-Biega (*V. hochstetteri* Schi-Bip., *V. kirungae* Rob. E. Fries; Yumoto et al. 1994; Augi. K. Basabose [Laboratoire de Primatologie CRSN, Lwiro, Congo], personal communication, 1997). At Tai, the bitter pith of *Paliosota hirsuta* (Thunb.) K. Schum. (Commelinacea) and *Eremospath macrocarpa* (Mann

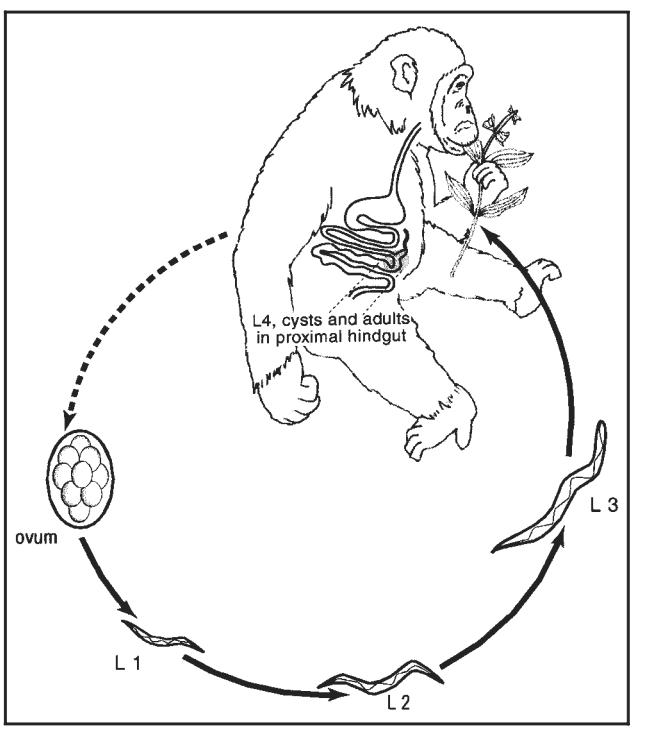

Figure 2. General life cycle of* Oeophagostomum spp.*, as exemplified in the chimpanzee (Huffman and Caton 2001). Eggs are laid at the 16–32 cell stage. While in the feces, the eggs rapidly develop into L1 rhabditiform larvae, hatching in as few as 24 hours under optimal conditions. The larvae feed on bacteria and molt to the L2 stage within 24 hours of hatching. Within 3–4 days after hatching, the L2 molt to become infective L3. L3 retain the protective cuticle of the L2 stage and are capable of surviving long periods of adverse environmental conditions (e.g., the hot, dry conditions of the dry season) in a state of dormancy. Infection occurs via ingestion of filariform L3 larvae that make their way onto vegetation eaten by the host. After ingestion, L3 larvae pass to the cecum, where they exsheath within approximately 3 days after ingestion. They then invade the tunica mucosa, stimulating the formation of separate cysts around individual larvae in the gut wall. In these cysts the larvae develop to the L4 stage, eventually returning to the lumen of the hindgut as immature adults. Once in the lumen, the larvae molt and reach the adult stage. Females begin to reproduce and deposit eggs about 1 month after infection.

Figure 3. Self-medicative behaviors. (a) Adult male JI with an Oesophagotsomum stephanostomum *infection chews on the bitter pith of* Vernonia amygdalina*. (b) Adult female LD is swallowing leaves of* Aspilia mossambicensis*. (c, e, f) Scanning electron micrographs (SEM) showing the characteristic bristly surface of the leaves swallowed whole by apes species, accompanied by pictures of each species (*Aneilema aquinoctiale, Trema orientalis, *and* Lippia plicata, *respectively). (d) This adult* O. stephanostomum *worm (approximately 2.5 cm) was expelled in the dung along with 20 others, together with 50 folded leaves of* A. aquinoctiale*, shown here. Photos: Michael A. Huffman. SEM: Thushara Chandrasiri.*

and Wendl.) Wendl. (Palmae) are chewed (Christophe Boesch [Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany], personal communication, 1996).

When ingesting the pith from young shoots of *V. amygdalina*, chimpanzees meticulously remove the outer bark and leaves to chew on the exposed pith, from which they extract extremely bitter juice and residual amounts of fiber (Figures 3a, 4a, 4b). The amount of pith ingested in a single bout is relatively small, ranging from portions 5–120 cm long by 1 cm in width. The entire process, depending on the amount ingested, takes anywhere from less than 1 to as long as 8 minutes. Mature conspecifics in proximity to individuals chewing *Vernonia* bitter pith (or leaf swallowing, described below) show no interest in ingesting the pith. Infants, however, have on occasion been observed to taste the pith discarded by their ill mothers. Thus, from a very young age individuals in a group are exposed to the plant-eating behaviors and to the plants and their context of use.

At Mahale, use of *V. amygdalina* has been recorded in all months except June and October in the late dry season (Nishida and Uehara 1983). Despite such broad availability, use of *V. amygdalina* by chimpanzees is highly seasonal, occurring mainly during the rainy season months of November, December, and January.

Impact of bitter-pith chewing on parasite load

In general, when an individual chews the bitter pith of *V. amygdalina*, that individual is in ill health, as evidenced by diarrhea, lethargy, weight loss, and nematode infection. In two cases recorded in detail, recovery from such symptoms was evident 20–24 hours after the individuals chewed the bitter pith (Huffman and Seifu 1989, Huffman et al. 1993). In one of these cases, the eggs per gram (EPG) of feces level of an *O. stephanostomum* infection could be measured; it was found to have dropped from 130 to 15 in 20 hours. Seven other individuals, monitored over the same period, had *O. stephanostomum* infections but were not observed chewing bitter pith; these individuals did not register such a dramatic drop in EPG. In these seven control cases, *O. stephanostomum* EPG levels actually increased over time. The rise in EPG levels represents the overall trend for increased reinfection by *O. stephanostomum* at the beginning of the rainy season (Figure 5). The ingestion of the bitter pith of *Vernonia* appears to affect nodular worm reproductive output and provide relief from symptoms of related gastrointestinal upset.

Ethnomedicinal and phytochemical evidence for the pharmacological effectiveness of bitter-pith chewing

The similarities between chimpanzees and humans in their use of *V. amygdalina* strengthen support for the effectiveness of bitter-pith chewing on parasite control and offer interesting insight into the common criteria for plant selection (Huffman et al. 1996a). For several African ethnic groups, a concoction made from *V. amygdalina* is prescribed treatment for malarial fever, schistosomiasis, amoebic dysentery, several other intestinal parasites, and stomachaches (Dalziel 1937, Watt and Breyer-Brandwijk 1962, Burkill 1985, Huffman et al. 1996a). The WaTongwe of Mahale use this plant as a treatment for intestinal parasites, diarrhea, and stomach upset. Ugandan farmers feed their pigs young branches and leaves of *V. amygdalina* to rid them of intestinal parasites. A number of bitter *Vernonia* species found across Africa, the Americas, and Asia are known both for their wide ethnomedicinal use and pharmacological effectiveness against gastrointestinal-related ailments, including parasite infections. As the name implies, *V. anthelmintica* is a clinically important traditional treatment in India for parasite infection.

Figure 4. (a)* Vernonia amygdalina*, or bitter leaf (b), is used in a traditional West African dish known in Cameroon as N'dole (c), which is prepared from the leaves of the plant. Photos: (a) and (b), Michael A. Huffman; (c), Koichi Koshimizu.

Phytochemical analysis of *V. amygdalina* samples collected at Mahale from individual plants known to be used by chimpanzees revealed the presence of two major classes of bioactive compounds (Figure 6). A number of known sesquiterpene lactones, and 13 new stigmastane-type steroid glucosides and their freely occurring aglycones, have been isolated (Ohigashi et al. 1991, Jisaka et al. 1992a, 1992b, 1993a, 1993b). The

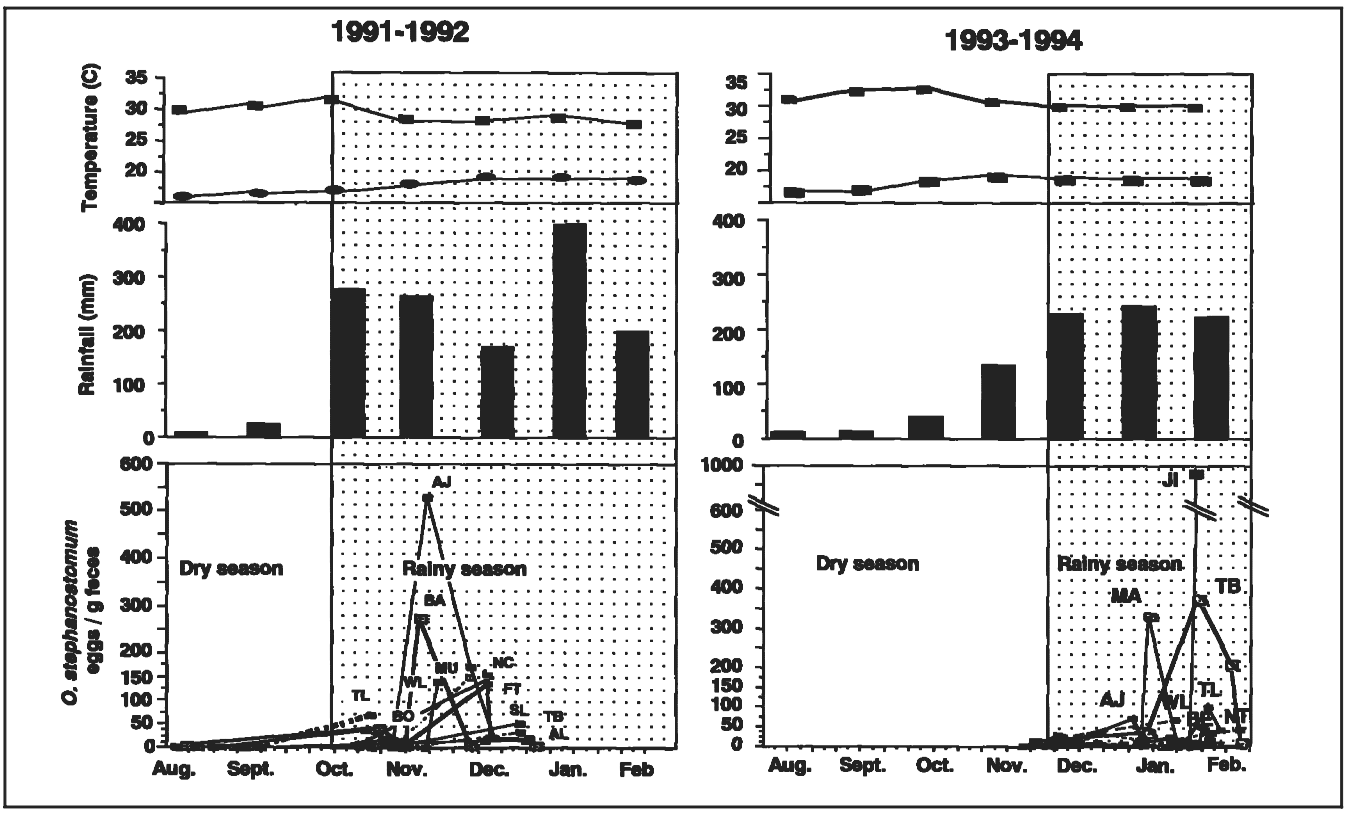

Figure 5. Seasonal variation in the infection levels of strongyle nematode **Oesophagostomum stephanotomum** *in Mahale chimpanzees. While infections are carried year round, reinfection in chimpanzees of western Tanzania occurs mainly during the rainy season. Reinfection, noted by a significant elevation in individual eggs per gram (EPG) counts, occurs approximately 1–2 months after the onset of the rainy season, regardless of which month the rains first begin (Huffman et al. 1997). This lapse in time corresponds with the 1-month prepatent period (period between when the parasite enters the host and when it begins to reproduce) of* **Oesophagostomum** *spp. (Anderson 1992). Arrested larval development occurs in* **Oesophagostomum** *spp. (Armour and Duncan 1987, Krepel et al. 1994), and at Mahale, shortly after the onset of the rainy season, the external environmental conditions of rising humidity and temperature become optimal for rapid development of the eggs and larvae. The markedly higher individual EPG levels at the beginning of the rainy season are thought to be caused by the increase in transmission of infective stage L3 larvae into the host from the moist environment.*

sesquiterpene lactones present in *V. amygdalina* are also found in *V. colorata* and in a number of other *Vernonia* species. They are well known for their anthelmintic, antiamoebic, antitumor, and antibiotic properties (Toubiana and Gaudemer 1967, Kupchan et al. 1969, Asaka et al. 1977, Gasquet et al. 1985, Jisaka et al. 1992a, 1993b). Crude methanol extracts of the leaves exhibited immunosuppressive activity and inhibition of the process that initiates the first stage of tumor cell growth (Koshimizu et al. 1993). The cytotoxic sesquiterpene lactones were found to be most abundant in the leaves and bark, the parts that chimpanzees at Mahale have always avoided. This is quite interesting, given that the leaves from wild growing plants can be lethal if ingested raw and in large amounts, as is sometimes observed among domestic goats in West Africa. That chimpanzees avoid these parts, yet domestic animals seem unable to do so, suggests a higher level of sophistication in chimpanzees' knowledge of plant secondary compounds and their beneficial use. People across western Africa soak leaves from the less toxic cultivated plant in water several times to reduce their bitterness and toxicity so they may be cooked with meat and eaten as a tonic food called N'dole in Cameroon (Figure 4c). The woody branches, which have noteworthy antibacterial properties, are used widely as chew sticks—the famous African "toothbrush."

In vitro tests on the antischistosomal activity of the plant's most abundant steroid glucoside (vernonioside B1) and sesquiterpene lactone (vernodaline) showed significant inhibition of movement of the adult parasites and of the adult parasite females' egg-laying capacity (Jisaka et al. 1992b). These findings are consistent with the observed decline in egg output of *O. stephanostomum* over a 20-hour period in one adult female chimpanzee at Mahale after her ingestion of *V. amygdalina* pith (Huffman et al. 1993). The sesquiterpene lactones showed significant in vitro plasmodicidal activity, while that of the steroid glucosides was weaker (Ohigashi et al. 1994).

Some of the species whose bitter pith is ingested by chimpanzees at Gombe, Kahuzi-Biega, and Tai also have a number of ethnomedicinal and pharmacological properties. *Vernonia colorata* and *V. amygdalina* are not distinguished from

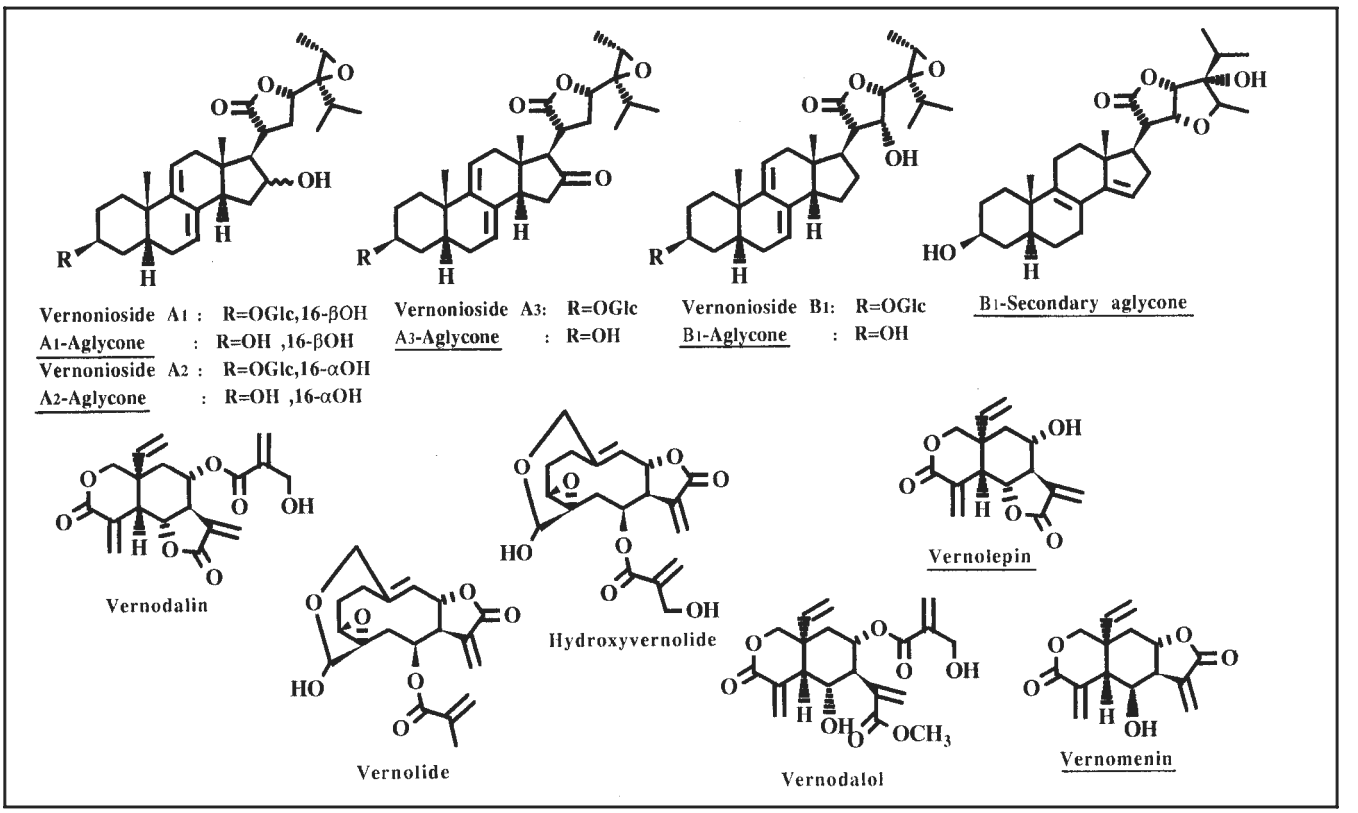

Figure 6. The steroid glucoside (upper row) and sesquiterpene lactone (lower row) compounds were isolated from the leaf, stem, pith, and root parts of* Vernonia amygdalina *specimens collected from Mahale National Park.

each other ethnomedicinally with regard to their medicinal properties and folk classification (Burkill 1985). Alkaloids occur in the pith as well as in the flower and leaf of *V. hochstetteri* (Smolenski et al. 1974). *Paliasota hirsuta* and *E. macrocarpa* are used in West Africa as a treatment for upset stomach, colic, and venereal disease and as an antiseptic and analgesic (Abbiw 1990, Neuwinger 1996). Moluscicidal activity has also been reported for *P. hirsuta* (Okunji and Iwu 1988).

Leaf-swallowing behavioral ecology

Leaf-swallowing behavior was first recorded for chimpanzees at Gombe and Mahale (Wrangham and Nishida 1983). Observers at both sites found the folded, undigested leaves of *Aspilia mossambicensis* (Oliv.) (Compositae), *A. pluriseta* (O. Hoffm.) Wild, and *A. rudis* Oliv. & Hiern in the dung of the chimpanzees, suggesting that leaf swallowing was unlikely to have any nutritional value and that chimpanzees may possess a sophisticated pharmacopoeia (Rodriguez et al. 1985). Other field researchers began to look for similar anomalous feeding habits among apes at their study sites. Currently, leaf-swallowing behavior involving more than 34 different plant species has been observed at 13 great ape study sites across Africa (Huffman 1997). The plant species used vary in life form (herb, vine, shrub, and tree), but the common property functionally linking all of these plants is their bristly, rough-surfaced leaves (Figure 3c, 3e, 3f). The distal half of leaves are selected one at a time, folded by the tongue and palate as they are slowly pulled into the mouth, and swallowed whole (Figure 3b). An individual may swallow anywhere from one to 56 leaves in one bout.

Longitudinal data on the temporal occurrence of leaf swallowing from both direct observations and the presence of leaves in the dung for *Aspilia* species at Mahale and Gombe demonstrate that leaf swallowing is an extremely rare behavior. Researchers have reported an average rate of use ranging from once every 69.0 hours (n = 18 bouts over 1242 hr) to once every 102.6 hours (n = 10 bouts during 1026 hours) for *Aspilia* species (Wrangham and Nishida 1983, Huffman 1997).

The species appropriate for leaf swallowing are available year-round at both Gombe and Mahale. Nonetheless, use is most common at Mahale after the beginning of the rainy season (November through May), with peak frequencies in January and February 10–12 times greater than those of other months (Wrangham and Nishida 1983). At Gombe, peak frequencies of use have also been observed in January, February, March, and May, but also once in July (Wrangham and Goodall 1989).

During a 4-month study at Mahale, nematode infection was demonstrated in 83% of all cases of leaf swallowing (10 out of 12 instances; Huffman et al. 1996b). Multiple-species infections were common, but *O. stephanostomum* species (78%) were most commonly associated with leaf-swallowing behavior, followed by *S. fuelleborni* (56%) and *T. trichiuria* (33%) species. Symptoms associated with infections by these nematodes (diarrhea, malaise, abdominal pain) were verified

from direct observation in seven of the eight chimpanzees at the time they swallowed the leaves (Huffman et al. 1996b, 1997).

Impact of leaf swallowing on parasite load and the proposed mechanism of expulsion

Oesophagostomum stephanostomum worms were found in only 4% of the 254 dung samples collected from individuals and observed in detail (Figure 3d). Their occurrence in the dung was limited to chimpanzees that displayed symptoms of malaise and diarrhea.

In 1993–1994, six of the nine dung samples found to contain worms also contained whole undigested leaves of *A. mossambicensis*, *Trema orientalis* (L) Blume (Ulmaceae), or *Aneilema aequinoctiale* (P. Beauve.) Loudon (Commelinaceae). The relationship between the presence of both leaves and nodular worms in the dung was highly significant (Fisher's exact test, two-sided, $p = 0.0001$; Huffman et al. 1996b). On average, 10 worms were recovered with 20 leaves per stool, at a rate of 0.54 worms per leaf expelled by leaf swallowing (Huffman and Caton 2001), indicating a strong relationship between leaf swallowing and the expulsion of nodular worms (Huffman et al. 1996b). All worms were alive and motile at the time of expulsion; therefore, no chemical nematocidal activity in these plants is suspected.

No data exist for total worm burdens of *O. stephanostomum* in wild chimpanzees, though reports on *O. bifurcum* in humans living in rural Togo and Ghana indicate that an individual has an average burden of 96 worms (standard deviation 89.06, range 12–300, $n = 12$) (Krepel and Polderman 1992). Estimating from the rate of worm-to-leaf expulsion calculated above, a chimpanzee would have to pass at least 176 leaves or engage in leaf swallowing on average 10 times over the rainy season to rid itself of a comparable worm burden. The actual number of leaves observed to be swallowed by an individual in a single case ranges from 5 to 55. This scenario strongly suggests that repeated swallowing of leaves by chimpanzees over consecutive days or weeks can have a significant impact on its overall worm burden, which may account in part for the observed decline in the *O. stephanostomum* egg burden of many individuals later in the rainy season (Figure 5).

The observed physiological response of the gut was to expel whole leaves approximately 6 hours after swallowing (Huffman and Caton 2001). Considering the details of the life cycle of *Oesophagostomum* (Figure 2), leaf swallowing most probably controls nematode infection in at least three ways: By (1) causing adult worm detachment and expulsion, (2) flushing out some of the incoming infective L3 larvae before they are able to exsheath and penetrate the mucosa, and (3) decreasing pathology of nodular cysts (and reducing discomfort) by inducing the emergence of juvenile L4 larvae into the lumen (Huffman and Caton 2001).

At Mahale, leaf swallowing and bitter-pith chewing are sometimes displayed by the same individual on the same day; they are likely to act synergistically in lowering *O. stephanostomum* infection levels. Like bitter-pith chewing, leaf swallowing at Mahale appears to affect only *O. stephanostomum*. *O. stephanostomum* adults inhabit the large intestine, where they attach themselves to the mucosal wall through the suction of the buccal capsule. This attachment is not permanent, and worms migrate around the large intestine in search of food and mates. *Strongyloides fuelleborni* (2 mm) and *T. trichiura* (30–40 mm), however, are smaller than *O. stephanostomum* and burrow into the mucosa of the small intestine and cecum, respectively, where they embed themselves firmly. They are not susceptible to mechanical removal by the leaves.

The hypothesis about control of nematode infection predicts that because nodular worm infections are self-limiting (reproductive adults do not reinfect the host), the infection may be controllable if a chimpanzee periodically reduces parasite numbers during the most likely period of reinfection. At Mahale, the peak period of reinfection by *O. stephanostomum* (after the onset of the rainy season, around December or January) was found to closely correspond to the time when chimpanzees most frequently swallow leaves and chew bitter pith.

At Kibale, Wrangham (1995) found that whole leaves in the gut also increase the probability that tapeworm proglottids will be shed. Whole leaves were found in dung during the 21 months of the survey, whereas leaves and tapeworms were found together in only 33% of these months. The greater overall occurrence of leaves in dung without tapeworms, however, suggests that the expulsion of proglottid fragments may not be a direct function of leaf swallowing. Wrangham (1995) proposes that the proximate stimuli for leaf swallowing as observed at Kibale could be abdominal pain caused by tapeworm infections, and thus leaf swallowing may function to alleviate pain. In this light, it is possible that chimpanzees were responding to discomfort caused by the presence of tapeworms in the intestines regardless of whether the fragments were being expelled. The relief of pain from parasite infection appears to be a significant stimulus for both bitter-pith chewing and leaf swallowing.

Chimpanzees' acquisition of self-medicative behaviors and the evolution of medicine in traditional human societies

The way in which proposed self-medicative behaviors are individually acquired by the African great apes is a challenging topic for investigation. To suggest that self-medication is a behavioral tradition leaves open questions about how the behavior started and how individuals become predisposed to ingest medicinal plants. At one extreme, animals may have an innate tendency to select appropriate plants when ill, so that the role of tradition is reduced to local enhancement (i.e., naive individuals have their attention drawn to plant species used by others; Huffman and Wrangham 1994). However, with leaf swallowing and bitter-pith chewing, the species being ingested is not the only question to be resolved; what parts of the plant are ingested and how must also be learned for the

behavior to be effective. Given the high degree of conservatism in chimpanzee feeding habits (Nishida 1987), random sampling of novel food items, especially when ill, does not occur frequently. Perhaps the traditional behavior began during a period of extreme food scarcity, when ill and hungry apes who were forced to try new foods recovered their health and associated their recovery with the new food item.

Selective association between taste and gastrointestinal illness is a widely accepted principle of taste-aversion learning among mammals (Revusky 1984). The learning mechanism of food aversion in response to induced sickness has been well documented in several animal species (Zahorik and Albro Houpt 1977, Rozin and Vollmecke 1986, Letarte et al. 1997). Although the highly adaptive significance of the reversed process—that is, being able to associate improved health with the ingestion of novel plants with medicinal properties—seems self-evident, such learning mechanisms have received little attention (Zahorik 1977). Obviously, this area greatly needs further investigation.

In nonhuman primates, important benefits come from social learning, which allows naive individuals to acquire information through the experience of others and over time to perfect the behavior themselves (Galef 1977, Fragaszy and Visalberghi 1996). If the effectiveness of a behavior in bringing about a positive change in health is recognized, then perhaps it will spread through the group, at first slowly but then more rapidly as it is passed on to the youngest members. At this stage, it may be just one more part of the mother's foraging and behavioral repertoire to be acquired. At Mahale and presumably elsewhere, initial exposure to self-medicative behaviors take place by individuals at an early age, not when they are ill but when they observe the behavior of those that are ill, usually their mothers (Huffman and Wrangham 1994). Young chimpanzees have been observed on several occasions to closely watch these behaviors and immediately thereafter to attempt to perform them on their own (Huffman and Seifu 1989, Huffman and Wrangham 1994). These biological and psychological processes make up the core of nonhuman primate behavioral tradition and, as Johns (1990) argues, they are the biological seeds of the human cultural practice of medicine.

From apes to humans

The strong similarities in plant selection criteria among the African great apes in response to parasite infection and gastrointestinal upset, and the common use of some plants by chimpanzees and humans to treat such illnesses, are tantalizing evidence for the evolution of medicine. Our earliest hominid ancestors may have exhibited some similarities in plant selection criteria with both extant apes and modern humans. Although the fossil record provides no direct evidence concerning the subtleties of feeding behavior and diet, it seems reasonable to hypothesize that early hominids would have displayed at least the range of extant ape self-medicative behaviors.

It appears that the fundamentals of perceiving the medicinal properties of a plant by its taste, smell, and texture have their roots deep in our primate history. A major turning point in the evolution of medicine is likely to have been the advent of language in early humans, which enabled people to share and pass on detailed experiences about plant properties and their effects against disease. Another major event in human history is the adoption of food preparation and detoxification technologies, which allowed humans to exploit a wider range of plant life as food. Johns (1990) argues that it was at this turning point that humans' dependence on plant secondary compounds increased, because those compounds disappeared from the daily diet when detoxification technology was employed. Simply put, removal of the disease-fighting prophylactic properties of some of these secondary plant compounds from the diet may have contributed to a rise in certain illnesses that otherwise would have been kept in check. This development may have driven humans toward the greater use of some plants specifically as medicine and the use of others as "food–medicine." Furthermore, with the skilled use of fire to boil, steam, vaporize, condense, or otherwise extract useful secondary compounds from plants, these compounds could be used in a greater variety of ways.

The current level of sophisticated medicinal practices in traditional human societies may be the product of the greater variety of diseases and stress brought about by the change in subsistence methods from hunting and gathering to dependence on domestic crops and livestock in a sedentary setting. In this light, our early modern human ancestors may have had a smaller pharmacopoeia, but not for lack of technical sophistication. More likely, there were simply fewer diseases and less stress. Furthermore, a worldwide increase in human population and population density enables diseases to pass from person to person more easily, perhaps selecting for greater virulence. Thanks to the technological advancements of modern medicine, the lives of millions of people are saved or prolonged every year. Yet it is also technological advancement that introduces changes in our diets and exacerbates stress in our lives, which in turn boost rates of the modern diseases that nations spend fortunes trying to cure.

Future directions

As was true for Babu Kalunde almost a century ago, the study of animal self-medication and ethnomedicinal practices may provide important leads to future sources of medicine. A closer look into the manner in which animals use natural plant products may, for example, provide novel insights into viable new strategies for suppressing or slowing down the rate of acquisition of chemoresistance by parasites that infect livestock and humans.

A strong movement is under way in many African nations to evaluate and integrate those traditional medicines shown to be effective into modern health care programs. My collaborators and I in Africa and elsewhere realize the importance and urgency of such efforts. Our multidisciplinary approach to this research, wherein the biological activity of novel,

plant-derived compounds is assessed against parasite species found across a wide range of hosts, maximizes the chances of success. At the same time we recognize the importance of preserving the intellectual property rights of individuals, regions, and countries to any new discoveries derived from indigenous plant material. One objective of this research is to integrate our results into local health care and livestock management systems so that locally available plants can be properly used to the benefit of all.

Recently, Mohamedi said that he had heard of a traditional healer located east of Mahale who was using mulengelele to treat AIDS patients. He cautioned that he had not tried it on patients himself, so he could not verify its effectiveness. My colleagues and I were investigating the properties of mulengelele root in the laboratory as this article was being prepared.

We all may have much to gain from the evolutionary wisdom of our primate ancestors and the wealth of traditional medicine. Africa, the birthplace of humankind, may also have been the starting point for the evolution of modern medicine. That continent too has an important role to play in the world's future.

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References cited

Abbiw DK. 1990. Useful Plants of Ghana. Kew (UK): Intermediate Technology Publications and Royal Botanic Gardens.

Anderson RC. 1992. Nematode Parasites of Vertebrates: Their Development and Transmission. Wallingford (UK): CAB International.

Anderson RM, May RM. 1982. Population Biology of Infectious Diseases. Berlin: Springer-Verlag.

Armour J, Duncan M. 1987. Arrested larval development in cattle nematodes. Parasitology Today 3: 171–176.

Asaka Y, Kubota T, Kulkarni AB. 1977. Studies on a bitter principle from *Vernonia anthelmintica*. Phytochemistry 16: 1838–1839.

Barnard CJ, Behnke JM. 1990. Parasitism and Host Behaviour. London: Taylor and Francis.

Billing J, Sherman PW. 1998. Antimicrobial functions of spices: Why some like it hot. Quarterly Review of Biology 73: 3–49.

Brack M. 1987. Agents Transmissible from Simians to Man. Berlin: Springer-Verlag.

Burkill HM. 1985. The Useful Plants of West Tropical Africa, Vol. 1. 2nd ed. Kew (UK): Royal Botanical Gardens.

Dalziel JM. 1937. The Useful Plants of West Tropical Africa. London: Kew Botanical Gardens.

Etkin NL. 1996. Medicinal cuisine: Diet and ethnopharmacology. International Journal of Pharmacology 34: 313–326.

Etkin NL, Ross PJ. 1983. Malaria, medicine, and meals: Plant use among the Hausa and its impact on disease. Pages 231–259 in Romanucci-Ross L, Moerman DE, Tancredi LR, eds. The Anthropology of Medicine: From Culture to Method. New York: Praeger.

———. 1994. Pharmacological implications of "wild" plants in Hausa diet. Pages 85–101 in Etkin NL, ed. Eating on the Wild Side. Tucson: University of Arizona Press.

Fragaszy DM, Visalberghi E. 1996. Social learning in monkeys: Primate "primacy" reconsidered. Pages 65–84 in Heyes CM, Galef BG, eds. Social Learning in Animals: The Roots of Culture. San Diego: Academic Press.

Freeland WF, Janzen DH. 1974. Strategies in herbivory by mammals: The role of plant secondary compounds. American Naturalist 108: 269–289.

Futuyma DJ, Slatkin M. 1983. Coevolution. Sunderland (MA): Sinauer Associates.

Galef BG. 1977. Mechanisms for the social transmission of acquired food preferences from adult to weanling rats. Pages 123–148 in Barker LM, Best MR, Domjan M, eds. Learning Mechanisms in Food Selection. Waco (TX): Baylor University Press.

Gasquet M, Bamba D, Babadjamian A, Balansard G, Timon-David P, Metzger J. 1985. Action amoebicide et anthelminthique du vernolide et de l'hydroxyvernolide isoles des feuilles de *Vernonia colorata* (Willd.) Drake. European Journal of Medicinal Chemistry and Theory 2: 111–115.

Glander KE. 1975. Habitat description and resource utilization: A preliminary report on mantled howler monkey ecology. Pages 37–57 in Tuttle RH, ed. Socioecology and Psychology of Primates. The Hague (Netherlands): Mouton Press.

———. 1982. The impact of plant secondary compounds on primate feeding behavior. Yearbook of Physical Anthropology 25: 1–18.

Hladik CM. 1977. A comparative study of the feeding strategies of two sympatric species of leaf monkeys: *Presbytis senex* and *Presbytis entellus*. Pages 324–353 in Clutton-Brock TH, ed. Primate Ecology. London: Academic Press.

Huffman MA. 1997. Current evidence of self-medication in primates: A multidisciplinary perspective. Yearbook of Physical Anthropology 40: 171–200.

Huffman MA, Caton JM. 2001. Self-induced increase of gut motility and the control of parasite infections in wild chimpanzees. International Journal of Primatology 22: 329–346.

Huffman MA, Seifu M. 1989. Observations on the illness and consumption of a possibly medicinal plant, *Vernonia amygdalina* (Del.), by a wild chimpanzee in the Mahale Mountains National Park, Tanzania. Primates 30: 51–63.

Huffman MA, Wrangham RW. 1994. The diversity of medicinal plant use by chimpanzees in the wild. Pages 129–148 in Wrangham RW, McGrew WC, deWaal FB, Heltne PG, eds. Chimpanzee Cultures. Cambridge (MA): Harvard University Press.

Huffman MA, Gotoh S, Izutsu D, Koshimizu K, Kalunde MS. 1993. Further observations on the use of *Vernonia amygdalina* by a wild chimpanzee, its possible effect on parasite load, and its phytochemistry. African Study Monographs 14: 227–240.

Huffman MA, Koshimizu K, Ohigashi H. 1996a. Ethnobotany and zoopharmacognosy of *Vernonia amygdalina*, a medicinal plant used by humans and chimpanzees. Pages 351–360 in Caligari PDS, Hind DJN, eds. Compositae: Biology and Utilization, Vol. 2. Kew (UK): Royal Botanical Gardens.

Huffman MA, Page JE, Sukhdeo MVK, Gotoh S, Kalunde MS, Chandrasiri T, Towers GHN. 1996b. Leaf-swallowing by chimpanzees: A behavioral adaptation for the control of strongyle nematode infections. International Journal of Primatology 17: 475–503.

Huffman MA, Gotoh S, Turner LA, Hamai M, Yoshida K. 1997. Seasonal trends in intestinal nematode infection and medicinal plant use among chimpanzees in the Mahale Mountains, Tanzania. Primates 38: 111–125.

Janzen DH. 1978. Complications in interpreting the chemical defenses of trees against tropical arboreal plant-eating vertebrates. Pages 73–84 in Montgomery GG, ed. The Ecology of Arboreal Folivores. Washington (DC): Smithsonian Institution Press

Jisaka M, Kawanaka M, Sugiyama H, Takegawa K, Huffman MA, Ohigashi H, Koshimizu K. 1992a. Antischistosomal activities of sesquiterpene lactones and steroid glucosides from *Vernonia amygdalina*, possibly used by wild chimpanzees against parasite-related diseases. Bioscience, Biotechnology, and Biochemistry 56: 845–846.

Jisaka M, et al. 1992b. Bitter steroid glucosides, vernoniosides A1, A2, and A3 and related B1 from a possible medicinal plant, *Vernonia amygdalina*, used by wild chimpanzees. Tetrahedron 48: 625–632.

Jisaka M, Ohigashi H, Takegawa K, Hirota M, Irie R, Huffman MA, Koshimizu K. 1993a. Steroid glucosides from *Vernonia amygdalina*, a possible chimpanzee medicinal plant. Phytochemistry 34: 409–413.

Jisaka M, Ohigashi H, Takegawa K, Huffman MA, Koshimizu K. 1993b. Antitumor and antimicrobial activities of bitter sesquiterpene lactones of *Vernonia amygdalina*, a possible medicinal plant used by wild chimpanzees. Bioscience, Biotechnology, and Biochemistry 57: 833–834.

Johns T. 1990. With Bitter Herbs They Shall Eat It. Tucson: University of Arizona Press.

Koshimizu K, Ohigashi H, Huffman MA, Nishida T, Takasaki H. 1993. Physiological activities and the active constituents of potentially medicinal plants used by wild chimpanzees of the Mahale Mountains, Tanzania. International Journal of Primatology 14: 345–356.

Krepel HP, Polderman AM. 1992. Egg production of *Oesophagostomum bifurcum*, a locally common parasite of humans in Togo. American Journal of Tropical Medicine and Hygiene 46: 469–472.

Kupchan SM, Hemingway RJ, Karim A, Werner D. 1969. Tumor inhibitors XLVII vernodalin and vernomygdin, two new cytotoxic sesquiterpene lactones from *Vernonia amygdalina* Del. Journal of Organic Chemistry 34: 3908–3911.

Letarte A, Dube L, Troche V. 1997. Similarities and differences in affective and cognitive origins of food likings and dislikes. Appetite 28: 115–129.

Murakami A, Ohigashi H, Koshimizu K. 1994. Possible anti-tumor promoting properties of traditional Thai foods and some of their active constituents. Asia Pacific Journal of Clinical Nutrition 3: 185–191.

———. 1996. Anti-tumor promotion with food phytochemicals: A strategy for cancer chemoprevention. Bioscience, Biotechnology, and Biochemistry 60: 1–8.

Neuwinger HD. 1996. African Ethnobotany: Chemistry, pharmacology, toxicology. London: Chapman and Hill.

Nishida T. 1987. Learning and cultural transmission in non-human primates. Pages 462–474 in Smuts BB, Cheney DL, Seyfarth RM, Wrangham RW, Struhsaker TT, eds. Primate Societies. Chicago: University of Chicago Press.

Nishida T, Uehara S. 1983. Natural diet of chimpanzees (*Pan troglodytes schweinfurthii*): Long-term record from the Mahale Mountains, Tanzania. African Studies Monographs 3: 109–130.

Ohigashi H, Jisaka M, Takagaki T, Nozaki H, Tada T, Huffman MA, Nishida T, Kaji M, Koshimizu K. 1991. Bitter principle and a related steroid glucoside from *Vernonia amygdalina*, a possible medicinal plant for wild chimpanzees. Agricultural and Biological Chemistry 55: 1201–1203.

Ohigashi H, Sakai Y, Yamaguchi K, Umezaki I, Koshimizu K. 1992. Possible anti-tumor promoting properties of marine algae and in vitro activity of wakame seaweed extract. Bioscience, Biotechnology, and Biochemistry 56: 994–995.

Ohigashi H, et al. 1994. Toward the chemical ecology of medicinal plant use in chimpanzees: The case of *Vernonia amygdalina* Del., a plant used by wild chimpanzees, possibly for parasite-related diseases. Journal of Chemical Ecology 20: 541–553.

Okunji CO, Iwu MM. 1988. Control of schistosomiasis using Nigerian medicinal molluscicides. International Journal of Crude Drug Research 26: 246–252.

Plotkin MJ. 2000. Medicine Quest: In Search of Nature's Healing Secrets. New York: Viking.

Polderman AM, Blotkamp J. 1995. *Oesophagostomum* infections in humans. Parasitology Today 11: 451–456.

Revusky S. 1984. Associative predispositions. Pages 447–460 in Marler P, Terrace HS, eds. The Biology of Learning. Berlin: Springer-Verlag.

Rodriguez E, Aregullin M, Nishida T, Uehara S, Wrangham RW, Abramowski Z, Finlayson A, Towers GHN. 1985. Thiarubrin A, a bioactive constituent of *Aspilia* (Asteraceae) consumed by wild chimpanzees. Experientia 41: 419–420.

Roepstorff A, Bjorn H, Nansen P. 1987. Resistance of *Oesophagostomum dentatum* infections in pigs to pyrantel citrate. Veterinary Parasitology 24: 229–239.

Rozin P, Vollmecke TA. 1986. Food likes and dislikes. Annual Review of Nutrition 6: 433–456.

Sherman PW, Billing J. 1999. Darwinian gastronomy: Why we use spices. BioScience 49: 453–463.

Smolenski SJ, Silinis H, Farnsworth NR. 1974. Alkaloid screening. V. Lloydia 37: 506–536.

Toubiana R, Gaudemer A. 1967. Structure du vernolide, nouvel ester sesquiterpique isole de *Vernonia colorata*. Tetrahedron Letters 14: 1333–1336.

Varady M, Petersen MB, Bjorn H, Nansen P. 1996. The efficacy of ivermectin against nodular worms of pigs: The response to treatment using three different dose levels against *Oesophagostomum dentatum* and *Oesophagotstomum quadrispinulatum*. International Journal of Parasitology 26: 369–374.

Watt JM, Breyer-Brandwijk MG. 1962. The Medicinal and Poisonous Plants of Southern and East Africa. Edinburgh (UK): E. and S. Livingstone.

Wrangham RW. 1995. Relationship of chimpanzee leaf-swallowing to a tapeworm infection. American Journal of Physical Primatology 37: 297–303.

Wrangham RW, Goodall J. 1989. Chimpanzee use of medicinal leaves. Pages 22–37 in Heltne PG, Marquardt LA, eds. Understanding Chimpanzees. Cambridge (MA): Harvard University Press.

Wrangham RW, Nishida T. 1983. *Aspilia* spp. leaves: A puzzle in the feeding behavior of wild chimpanzees. Primates 24: 276–282.

Wrangham RW, Waterman PG. 1981. Condensed tannins in fruits eaten by chimpanzees. Biotropica 15: 217–222.

Yumoto T, Yamagiwa J, Mwanza N, Maruhashi T. 1994. List of plant species identified in Kahuzi-Biega National Park, Zaire. Tropics 3: 295–308.

Zahorik DM. 1977. Associative and non-associative factors in learned food preferences. Pages 181–199 in Barker LM, Best MR, Domjan M, eds. Learning Mechanisms in Food Selection. Waco (TX): Baylor University Press.

Zahorik DM, Albro Houpt K. 1977. The concept of nutritional wisdom: Applicability of laboratory learning models to large herbivores. Pages 45–67 in Barker LM, Best MR, Domjan M, eds. Learning Mechanisms in Food Selection. Waco (TX): Baylor University Press.