霊長類の自己治療行動—予防と治療

Self-Medication in Primates- Prevention and Cure

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Good morning everybody. First of all, I would like to express my thanks to all the people who have been involved in planning and hosting this highly significant international conference, beginning with Prof. Murata. Yesterday, I heard a lot of talks, and although they addressed fields somewhat different to my own, I still found them very interesting and informative. I enjoyed them a great deal.

I would like to talk to you now about my own research. My talk will overlap to some extent with what Prof. Murata was talking about earlier so let me introduce that part from now.

Today I am going to talk on the subject of "Self-Medication in Primates - Prevention and Cure". To begin with, there is one point on which I must insist. Many people may think that primates are capable of self-medication because they are clever. But I personally don't think this reasoning is correct. As Prof. Murata stated earlier, we humans too are animals. We shouldn't forget that just like us, plants and other animals are living things, and that we all live together in one world. With regard to self-medication, I don't believe that primates lead a particularly special kind of existence. On the contrary, I believe that all living things must perform self-medication in some way or another. Because unless organisms - whether they be primates, birds, fish, or even insects - have some means of maintaining their own health when facing disease or stress, then they would not be able to continue to exist on Earth.

Probably, the first living things to begin practicing self-medication were the plants, because predators eat plants if they can't protect themselves. Plants rely on their leaves to collect energy yet the parts of plants that have a lot of nutritional value, such as the leaves, are also the parts that get eaten by animals. Plants are considered to employ two strategies in order to defend themselves against being eaten. Their first defense strategy is to produce various chemical substances. Due to the presence of toxic secondary metabolites, important parts of many plants are rendered distasteful to animals. Many of these substances are bitter to the taste. For instance, if a predator overeats a certain kind of leaf and the animal develops a disorder (such as bad digestion, etc.) it will, as a result, tend to avoid feeding on the species of plant in question. The second strategy is a physical defense. Some plants grow large burs or thorns, while others have almost invisible small, hard projections that are closely packed on the surface of their leaves. These small projections, which make the rough textured surface of the leaves, are made of a glassy substance called silica which is very difficult to digest. So if an animal eats such leaves, it will develop indigestion.

This is a photograph of the surface of such a leaf taken though an electron microscope. It gives a good idea of how many tiny burs cover the leaf surface.

In short, third parties have taken over these two methods of defense, which originally evolved in order to protect plants, for use in protecting their own bodies. There are reports that many kinds of animals use these two plant defense methods as "medicines". Insects are considered to have been the first animals to begin self-medication as an evolutionary process. Around the time the first flowers and fruit began to grow, there was also an explosive increase in the number of insect species. In the course of that process, insects began using the plants for purposes other than nutrition. Plants were also co-evolving with insects, and relationships of deep

mutual dependence developed between the two.

This figure illustrates such close relationships between specific plants and insects. Some species of plants and insects have co-evolved into relationships of mutual dependence such that neither would be able to continue existing without the other. Ecosystems in which a single species of plant and a single species of insect function as a single unit have formed.

Within these relationships, insects play a role in making plant reproduction possible by carrying pollen. Of course, from the insects' standpoint, they are using the plants as a source of nutrition. And they also use the plants as "natural medical foods", which means they literally ingest medicinal plants. While on the one hand the insects help the plants, after ingesting the nutrition of the plant, they also use them to stimulate various functions by accumulating the plants' secondary metabolites within their own bodies. These secondary metabolites serve a variety of functions. For example, insects use them to stimulate various interactions between individuals of the same species, such as their function as precursors in the formation of pheromones. These help the sexes come together for mating. Some insects also use secondary metabolites as social communication tools or for defense against natural enemies. They make themselves unpalatable to predators by accumulating large amounts of these substances in their bodies. So if a predator puts an insect (such as a butterfly, which has adopted the defense strategy) into its mouth, the presence of the substance will cause the predator to spit out the insect. In that way, the insect can avoid being eaten. In addition, some insects use secondary metabolites for their anti-parasitic effects. Poisonous substances created in plants and ingested by the insect can function to destroy parasitic infections.

From insects to primates, many animals have been observed to practice self-medication. Animals try to protect themselves and maintain their health on several levels when they come into contact with diseases. Now I am going to change the subject to the self-medicative behavior of primates, and in particular, of chimpanzees.

I'd like to introduce you to how chimpanzees maintain their own health using the two kinds of plant defense systems I mentioned earlier, as well as to various other kinds of behavior they engage in to maintain health. Roughly speaking, these behaviors can be considered as operating on three levels.

Level 1 is behavior aimed at avoiding becoming infected with disease-causing agents and at reducing contact with such agents.

Two examples of this behavior are shown in these photographs. The one on the left shows olive baboons that live in the savanna on the Serengeti Plain.

There are four individuals and at dawn they go out foraging. Overnight, they stay in different trees, moving from one to another every few days. At times when food is plentiful they may remain on the same tree for a number of consecutive days. When they do this, a parasitic infection begins to break out from the excrement they leave beneath the tree. Sometimes it takes a few days for the infection to begin, but if the baboons climb the same tree everyday or carry out activities on the ground beneath the tree, the probability that they will contract the infection becomes very high. It is said that the baboons change the place where they stay overnight periodically in order to minimize that risk.

The other example I want to show you is the method illustrated in the photograph on the right. These monkeys are hamadryas baboons that live on the Arabian Peninsula. Their habitat is a desert area that doesn't have an abundant supply of water all year round. When water levels become very low, all the animals in the area gather close to the limited water sources. Due to the small volume of the water, the temperature of the water rises, creating a perfect environment for disease-causing agents (carried by the various animals in the area) to propagate. By drinking this water, animals have a very high probability of coming into contact with a wide range of pathogens. These baboons do a very clever thing in order to avoid the problem. In this photograph, you can see green

water flowing slowly at the bottom of the picture. The baboons are digging a hole in the sand at a place some distance from this stream. The groundwater emerges at the place where the baboons dig their hole. By making something like a well they are able to obtain cleaner water.

Through these two examples, we can ascertain that monkeys know some ways of avoiding being infected by disease and of reducing the risk of coming into contact with pathogens.

At level 2, animals eat foods that are nutritious and produce medicinal effects. In terms of the way humans look at the world, these foods fall into what we call the 'supplements' and 'spices' categories.

As you can see from this photograph, chimpanzees follow a largely frugivourous diet and they can quickly gain energy this way. The sugars contained in fruits can be used as an immediate energy source. Many fruits are also rich in protein and provide the animals with necessary fiber and minerals too.

On the other hand, chimpanzees also eat plants that contain various other ingredients in addition to nutrients at certain times of the year. These plants are classified as medicinal foods. Some plants contain substances that have bactericidal effects or which inhibit parasitic infections.

For example, for many years I have been conducting research on chimpanzees in the Mahale Mountains National Park in Western Tanzania. In that park, I have focused on a group called the M Group and researched how much of these medicinal foods are included in the food they actually eat. In the course of this research, I have found that approx. 22% of the 172 kinds of food they usually eat coincide with natural medicines that humans use to ward off parasitic infections. More generally, it has been established that throughout Africa both chimpanzees and humans use the same parts of the same plant species for easing specific symptoms of specific diseases such as parasitic infections or gastrointestinal diseases. Interestingly, apart from fruit, people in Africa use many other plant parts such as leaves and leafy stems, trunks, seeds, etc., as medicinal plants.

Now, I will show the situation with another primate species, the gorillas. In the same way as I did with chimpanzees, I surveyed how much overlap there was between the plant parts that gorillas eat and the plants that local people use for medicines, with reference to a list compiled of all the foods known to be eaten by the three sub-species of gorillas. Surprisingly, I found that the plan parts taken by both gorillas and humans contain substances that have a variety of effects. For example, some of them contain factors that inhibit the growth of cancers, promote cardiac function, work as stimulants, boost the immune response, etc., in addition to working as antiseptic, anti-parasitic and antiviral agents. Unfortunately, it has not yet been observed how much, in what way, or in what situations gorillas use these plant parts.

The next level up is Level 3. At this level, primates are using medicinal plants precisely as humans use medicines. This is self-medicative behavior in which primates are observed to use medicinal plants when they are sick or when disease symptoms appear. In cases where large amounts of the plants are poisonous, they use limited amounts and employ special methods to treat disease. Even if their health condition deteriorates, they only use limited small amounts of these plants.

Now, let me explain how this works in the case of chimpanzees. They have two ways of self-medicating that I would like to introduce.

In the photograph on the left side of the slide, you can see a chimpanzee named Linda, who is about to put a leaf into her mouth. The plant is of the genus Aspilia, which has leaves with a roughly textured surface similar to the one I showed you in the electron microscope photograph earlier.

Chimpanzees put the leaves into their mouth one by one, rolling each leaf around in their mouth and then

swallowing it without chewing it. Sometimes they may swallow up to a hundred leaves in this way at a single sitting. As I mentioned earlier, such leaves are difficult to digest. Chimpanzees eat things that are hard to digest in order to promote the body's rejection responses. When the leaves pass through the digestive system, they act as a de-worming agent, helping to remove the parasitic nematode worms that infest the chimpanzees' intestines. This self-medication method involves a physical effect, and the chimpanzees' are engaging in what is known as "leaf swallowing behavior".

Another method is to use Vernonia amygdalina, a plant in the family Asteraceae. The chimpanzees chew on the bitter pith of the plant aggressively and suck out its juice. This is known as "bitter pith chewing behavior". This pith juice doesn't contain anything of nutritional value, but it is effective for treating oesophagostomiasis, an illness resulting from a parasitic nodular worm infection. This infection is quite a serious disease, but based on my own observations, by drinking the bitter juice of the pith of this plant, visually confirmable symptoms such as fatigue, decreased appetite and abnormally colored urine disappeared within 24 hours, and the parasites' egg laying activities also ceased. I have reported this observational data in scientific journals.

In the Mahale Mountains National Park, there are clear differences in how the nodular worm infection rates wax and wane between the rainy and dry seasons. Within the approximately six months when the region receives heavy rain, these parasites actively and repeatedly infect chimpanzees.

This figure shows the life cycle of the nodular worms. When the chimpanzees excrete the eggs of these worms, they remain in the soil or on the surface of low plant leaves until they reach the L3 stage. At this stage they become larvae capable of re-infecting chimpanzees. About the time when the rains start, the environment becomes favorable for the development of the eggs and young larvae excreted in chimpanzee feces. When chimpanzees unknowingly take in the infectious L3 stage larvae, these parasites burrow into the chimpanzee intestinal wall and produce nodules. After an incubation period of about one month, the negative effects of the infection appear in the chimpanzees. If the degree of infection (the number of adult worms infecting the host) becomes very high this leads to symptoms such as intestinal inflammation, diarrhea, stomach pain, etc. If the infection is particularly heavy, it may even kill the host chimpanzee. In the period from the beginning to the middle of the rainy season, infected chimpanzees frequently engage in both bitter pith juice ingestion behavior and leaf swallowing behavior.

Sick individuals carry out these two activities frequently and interchangably. Though as I mentioned above, because Veronia is toxic, they do not practice this behavior as much as leaf swallowing. Now, I will introduce the behavior in more detail.

This photograph shows a chimpanzee putting a leaf into its mouth, rolling it around and trying to swallow it in a gulp.

I once rolled up such a leaf and attempted to swallow it in the same way as the chimpanzees do, but it was extremely difficult. The burs grow downward, so the leaves tend to stick in the throat and will not travel down smoothly. It was a thoroughly unpleasant experience for me. However, chimpanzees casually swallow up to a hundred of these leaves on occasion.

The chimpanzee in this photograph is again Linda. She is about to swallow the leaf she is holding in her hand. The other photograph shows a leaf on which you can see an adult modular worm of the species Oesophagostomum stephanostomum, which is about 3cm in length. Fighting infestations by this parasite is one of the aims of this particular form of chimpanzee self-medication.

On average, two leaves is effective in expelling one worm. Sometimes, 20 to 30 adult worms are forced out from a single 'dose' of 40~60 leaves. The de-worming effect is not due to the plant's secondary metabolites but the result of transient diarrhea simply increasing

movements of the intestines, which rapidly expel the leaves and worms with them. Even if the chimpanzees ingest the leaves every day, it doesn't seem to cause them any problems. During the rainy season, there is a high possibility that individual chimpanzees will be infected by parasitic worms many times, but this method seems to be sufficient for controlling the number of worms. Looking at the infection rates data, the treatment seems to have this effect.

Chimpanzees engage in this behavior frequently at the beginning of the rainy season when each individual's modular worm infection burden increases. Not every individual chimpanzee becomes infected, and this behavior is not observed everyday in the rainy season. But in the dry season it is hardly observed at all. However, from about one month into the rainy season, a marked increase is observed in bitter pith chewing behavior.

As research into the African great apes - chimpanzees, bonobos and gorillas - has progressed over the past 20 years, this leaf swallowing behavior has been observed at 16 research sites, not only at Mahale. The same behavior has also been noted at many sites being used to counter infection by the nodular worm Oesophagostomum stephanostomum. Yet another target of the same behavior is the tapeworm Bertiella studeri. Leaf swallowing behavior has a similar de-worming effect on both infections. The adult stage worms and the tapeworm proglottids are excreted together with the leaves. In the case of the nodular worm, the number of adult-stage worms is clearly reduced, so there seems to be a definite effect. As for the tapeworm nodule excretion effect, there has not been much discussion on the subject. Up to now, it has been established that chimpanzees engage in leaf swallowing behavior while making use of the leaves of about 40 different species of plants. All of these species have similarly rough textured leaves.

Next, let's take a closer look at the chimpanzees' bitter pith juice ingestion behavior. The plant they use at Mahale is Vernonia amygdalina. This plant is very well known in both folk medicine and in pharmacognosy. It has been demonstrated to lower malarial fever, blood cholesterol and blood sugar levels, and is very effective against parasitic infections. People are widely reported to use it for their own livestock. However, although this plant has been studied for a century, the fact that primates use it as a medicine for treating parasitic infections was not discovered until 1987. It was in fact myself who made the first observation and reported about this behavior. Interestingly, I found that both humans and chimpanzees exhibit the same symptoms after ingesting Vernonia amygdalina. The plant is very bitter. When people use it, they first beat it and then soak it in water until the water becomes deep brown, which doesn't take very long. Then they drink the water down all at once. This is said to result in an improvement in their condition within 24 hours.

In the case of chimpanzees also, within about 24 hours of drinking the bitter juice from the pith of the plant, their body condition shows clear signs of improvement. By observing their behavior we can clearly see improvements in their appetite and physical strength. The fact that humans and chimpanzees have this response in common is very interesting.

People have been researching Vernonia amygdalina as a natural compound for over a hundred years. A long list of compounds have been extracted from the plant, with many kinds of sesquiterpene lactones among them. Every report without exception mentions the powerful activity and poisonous ingredients of the plant.

However, until 1987, nobody had paid attention to the plant pith, the part that is used by chimpanzees, so the chemical composition of the pith was unknown. To remedy this situation, I carried out joint research with Prof. Koshimizu and Prof. Ohigashi of the Faculty of Agriculture at Kyoto University regarding the chemical analysis of Vernonia amygdalina and its bioactivity. One of the results of the research was that we discovered 13 new chemical compounds. These were identified to be steroid glucosides and were named Vernonioside A1, 2, 3, 4, B1, 2, 3, etc.

In summary, chimpanzees engage in leaf swallowing

and bitter pith juice ingestion behaviors as self-medication during the rainy season when infection rates of the nodular worm Oesophagostomum stephanostomum and the tapeworm Bertiella studeri are high. Other medicinal plants are also used intensively throughout the rainy season when parasite infection rates peak. The chimpanzees appear to use these plants from time to time up until the end of the rainy season.

In the dry season, leaf swallowing and bitter pith juice ingestion behavior are rarely observed. And the chimpanzees reduce their intake of natural medicinal foods too. When the season changes, the animals change their food menu and employ more direct treatment methods.

Lastly, I would like to talk about ethnopharmacognosy, which is another of my research themes. In this connection I would like to introduce you to Mohamedi Seifu Kalunde, with whom I cooperate on chimpanzee research in Tanzania. Mohamedi is very knowledgeable about medicinal plants and he works actively as a traditional healer treating the diseases that affect the local people. He was born and raised in the forests of the Mahale Mountains, and has a wealth of knowledge about local medicinal plants that has been handed down for generations in his family. I've walked around the forest together with Mohamedi for almost 20 years and he has taught me a great deal about chimpanzees and plants. For example, he has told me that among his own relatives there are people who tell how they obtained many new medicines by observing how sick animals act. Even while we were working together, he discovered a new antidiarrhetic medication. Having seen a sick chimpanzee with diarrhea practicing self-medication he correctly surmised that the plant being used might be effective for people too. So he tried it out on himself and found that it did work well. It is widely used nowadays.

I have another interesting story to relate, this time about Babu Kalunde, Mohamedi's grandfather, who was a traditional healer. He discovered a new drug just by watching the strange behavior of a porcupine. He noticed a weak porcupine digging up and eating the root of a plant his tribe called mulengelele which he recognized as being highly poisonous. Babu Kalunde knew there must be a reason behind the behavior so he brought a few roots back to his village and used them to treat some seriously ill patients. Mohamedi and other healers still use this root today to treat infections for which western doctors would use antibiotics.

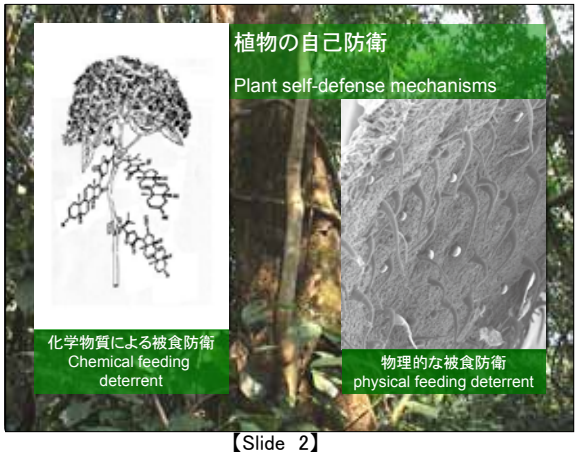
The next speaker, Prof. Tsuda, will be talking about malaria, so I'm going to end my talk by giving a brief introduction to primate malaria. There is no doubt that malaria has had a huge effect on primates as well as on humans. It is an established fact that all four malaria species infecting humans are derived from strains that infect non-human primates. Recently, in Southeast Asia, the simian malaria parasite Plasmodium knowelsi (which usually only infects macaques) has begun infecting humans too. Since this is an infectious disease that the local monkeys have been living with for a long time, it does not represent a major problem for the monkeys. But as an emerging disease in humans, it causes serious symptoms in people who contract it.

At present, there are no effective medicines for treating the disease but in the course of recent research it has been found that chimpanzees are also infected by malaria. As part of our 1990s research into the ingredients within the medicinal plant Vernonia amygdalina - as used by chimpanzees - we have discovered that chemical compounds have a strong anti-malarial action. More recently, another chemical compound has been reported which also has anti-malarial parasitic action. It was isolated from a species of plant called Trichilia rubescens and it is a plant that chimpanzees in Uganda use. So there is great anticipation that this discovery can be turned into a new medicine for people.

Several years ago I checked out the latest reports about Vernonia amygdalina (using Google) and found that the University of Missouri had obtained a patent to use a substance obtained from this plant as a medicine for treating breast cancer. Animals and humans have been living together for a long time in one world but since

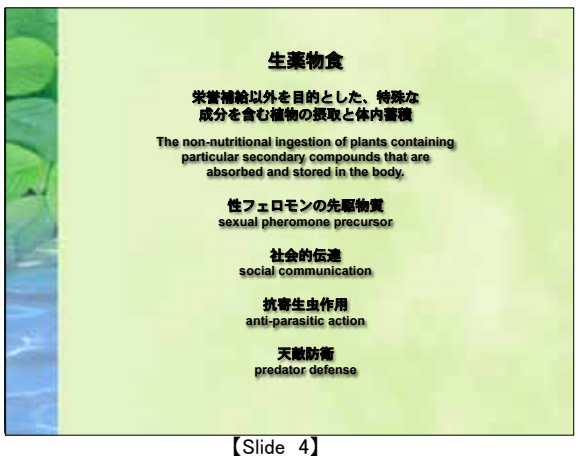
we humans have come to live in modern societies we have gradually lost touch with nature. As a result we have started to lose the natural knowledge that we had previously gathered. I believe there is a link between preserving the natural environment and biodiversity and protecting our own health. We need to reconsider the importance of the global environment and our position in nature. In closing I would like to thank you very much for listening.

【Slide 1】



【Slide 2】

【Slide 3】



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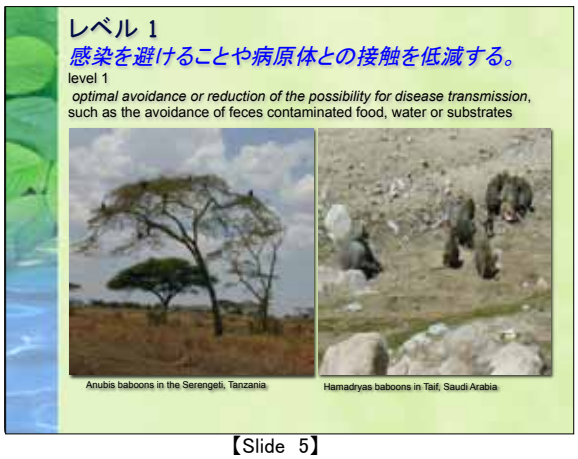
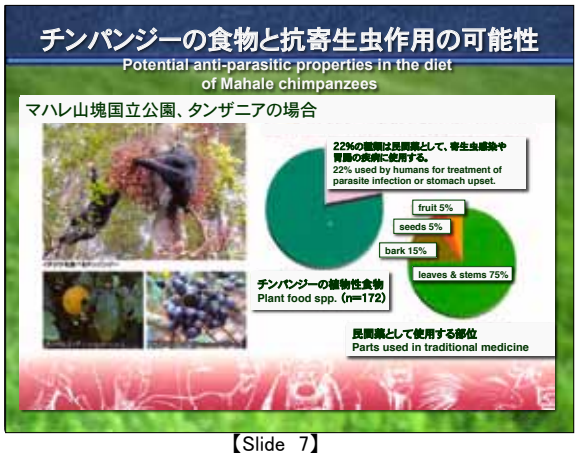


【Slide 5】

【Slide 6】



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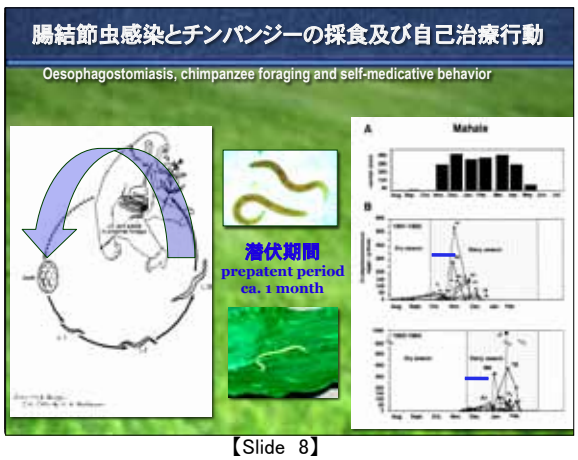

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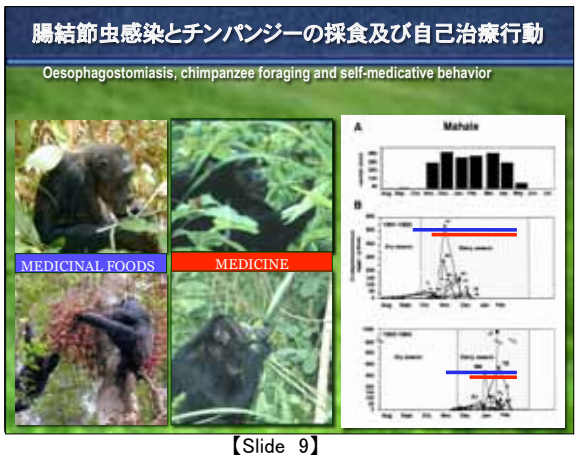


【Slide 9】

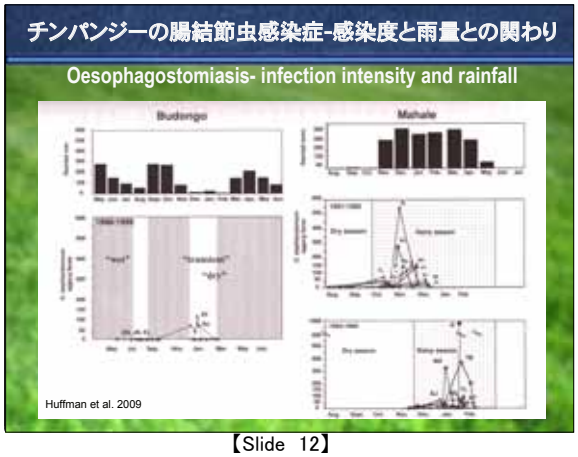
【Slide 13】

【Slide 10】

【Slide 14】

【Slide 11】

【Slide 15】

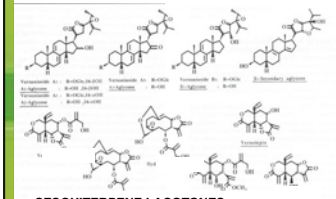


【Slide 12】

【Slide 16】

ベルノニアから単離された新成分
New compounds isolated from Vernonia amygdalina

STEROID GLUCOSIDES
vernonioside



SESQUITERPENE LACOTONES

vernodaline　hyrdroxyvernolide　vernolopin
vernolide　vernodalol　vernomenin

vernonioside:
発見された新成分の分離群
Newly discovered class of compounds

sesquiterpene lactones:
ベルンイア の多くの種に存在が確認されている。
Widely reported in Vernonia ssp.

【Slide 17】

ベルノニアに含まれている成分の抗マラリア採用
Anti-malarial properties of Vernonia

TOWARD THE CHEMICAL ECOLOGY OF MEDICINAL PLANT USE IN CHIMPANZEES: THE CASE OF *Vernonia amygdalina*, A PLANT USED BY WILD CHIMPANZEES POSSIBLY FOR PARASITE-RELATED DISEASES

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【Slide 18】

トリキリアの抗マラリア活性
Anti-malarial properties of Trichilia

Novel Antimalarial Compounds Isolated in a Survey of Self-Medicative Behavior of Wild Chimpanzees in Uganda

【Slide 19】

サルマラリア　ヒトマラリア

【Slide 20】

ヒトマラリア　サルマラリア

Human Malaria Ape　**Macaque Malaria**

Plasmodium falciparum　<----------　P. reichenowi, P. gaboni
(ゴリラ由来 gorilla origin)

P. vivax　<----------　P. simium
(アジアのマカク由来　Indian - Asian primate origin)

P. ovale　<----------　P. ovale variant type
(チンパンジー由来 chimpanzees origin)

P. malariae　<----------　P. knowlesi
(マカク由来　Macaque origin)

P. knowlesi
新人獣共同感染症 Newly emerging zoonoses

【Slide 21】

サルまね?
Human see, human do?

【Slide 22】

タンザニアの伝統医が野生動物の行動観察から新薬の発見をする。

Traditional healers in Tanzania acquire new medicines from the observation of wild animals

【Slide 23】

【Slide 24】


ベルノニアから乳がん治療の研究が行われている。
In 2004, a patent was registered in the US by researchers at Jackson State University, Missouri for the phytochemotherapeutic applications of *Vernonia amygdalina*. Plant extracts demonstrated inhibitive activity against growth of neoplastic cells, including those of human breast cancer.
United States Patent
US 6,849,604 B2
Feb. 1, 2005

【Slide 25】