Nine

Medicinal Pepper

THE ANCIENT ALLURE OF PEPPER AS A MEDICINE IS ATTRACTING ATTENTION TODAY. SCIENTISTS IN THE WEST ARE INTRIGUED BY PEPPER'S ABILITY TO QUELL INFLAMMATION. EXPERIMENTS SUGGEST THE SPICE COULD HAVE A ROLE IN COMBATING CANCER. BETEL, ONE OF PEPPER'S SIBLINGS, APPEARS TO BE A PROMISING TREATMENT FOR THE PARASITIC DISEASE LEISHMANIASIS.

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"Piper nigrum *L. (Piperacea) has insecticidal properties and could potentially be utilized as an alterative to synthetic insecticides."*

—*Journal of Agricultural and Food Chemistry*

"Traditional plant remedies, particularly those used in traditional Chinese medicine and Indian Ayurvedic medicine have, in many cases, been observed to yield positive results."

—*Planta Medica*

"Many physiological effects of black pepper, its extracts or its major active principle, piperine, have been reported in recent decades."

—Krishnapura Srinivasan, Department of Biochemistry and Nutrition, Central Food Technology Research Institute, Mysore, India

The healthful properties attributed to pepper some four hundred years ago—its ability to soothe the lungs, vanquish fevers, ease a variety of aches and pains, and even reduce the size of tumors—is gaining traction today. Thanks to the growing interest in natural products in the West, a small renaissance in the study of pepper as a medicine is under way. The spice and its *Piper* siblings still inspire our curiosity and enterprise, and perhaps one day a derivative of black pepper will become an important medicine for the treatment of cancer or other diseases.

Scientists in the United States, Britain, and Italy are now testing pepper's potency as an anti-inflammatory and antimicrobial agent; an anticancer therapy; a preservative; an insecticide; an antioxidant; an analgesic; and a treatment for vitiligo, a skin pigmentation disorder. A small number of studies in scientific journals even suggest that pepper could improve mood and slim the waistline. In Japan, researchers are evaluating whether inhaling the aroma of black pepper oil, which is used in the fragrance industry and is not pungent, can improve swallowing by stimulating parts of the brain in elderly people who have suffered strokes. They hope to prevent prevent aspiration pneumonia, a common cause of death in these patients. The Japanese are also evaluating whether the smell of pepper oil can stimulate other parts of the brain to help people quit smoking.

And in China, where pepper has long been used as a folk remedy for the treatment of epilepsy, chemicals derived from the spice are now incorporated into medicines to treat epileptic seizures in children.

By far, though, the property that is drawing the most scrutiny is pepper's tendency to act as a sort of booster, or biological enabler, of medicines. In this role, the spice helps make medicines more "bioavailable" by increasing the amount of the drugs in the bloodstream and helping them to remain longer in the body. The liver and the intestine often throw up barriers that prevent medicines from doing

their job. The usual culprits are metabolic enzymes that chew up medicinal compounds before they can be absorbed in the body, rendering them less useful. In the mid-1980s, a team in India discovered that piperine, a compound that is abundant in black pepper and which gives the spice its famous kick, inhibited the activity of certain enzymes in the liver and intestine. This finding sparked an interest in piperine's propensity to make medicines more effective.

Since then a number of clinical studies have shown that piperine boosts the levels of phenytoin for epilepsy, propranolol for high blood pressure, theophylline for asthma, rifampin for tuberculosis, and nevirapine for HIV infection, among other medications. The ability of black pepper to make drugs more bioavailable may be the main reason why an herbal mixture called *trikatu* is so widely prescribed along with other treatments in Ayurvedic medicine, a system that aims to prevent disease and promote well-being. By enhancing the effects of these other medicines, trikatu would serve as a sort of all-purpose medicinal amplifier.

More than three hundred citations for scientific papers related to black pepper are in PubMed, the huge database maintained by the National Library of Medicine. The scientific work on black pepper is proving that it possesses properties that have long been exploited in Ayurvedic medicine. This system of healing has not been embraced in the West, although other alternative or complementary medicines from Asia are becoming more popular in Western countries. The British attempted to rid India of Ayurvedic medicine altogether, when, in 1835, they banned teaching the system in India. More recently, in 2000, the House of Lords issued a report saying that there wasn't evidence to support Ayurvedic's role in the diagnosis and treatment of disease. A recent review of studies involving some 166 plant

species—from sage leaves, cinnamon, and fenugreek to nutmeg, dandelion, and white sandalwood—utilized in Ayurvedic medicine presents a different picture. The survey by Sarah Khan and Michael Balick, an ethnobotanist at the Institute of Economic Botany at the New York Botanical Garden, reveals that 43 percent of the plants had undergone testing in at least one human clinical trial and 62 percent had been evaluated in studies in animals. Although the authors acknowledge that many of the studies lack the appropriate rigor associated with the "gold-standard" of clinical testing in the West, such as adequate sample size and controls, their review suggests which plant species might be suitable for larger and better-controlled clinical trials. They conclude that the studies in the scientific and medical literature dispel "the all-too-commonly held notion that no clinical or other evidence exists to support the use of plants used in traditional medical systems."

Spices were frequently mentioned in ancient Ayurvedic texts, and some seven hundred drugs derived from pepper, turmeric, ginger, cinnamon, and other spices were described by a physician named Sushruta the Second in about 500 B.C. It isn't surprising that people who were surrounded by spice plants found extensive uses for them. In ancient times, black pepper was a remedy for constipation, diarrhea, earache, heart disease, hernia, indigestion, liver problems, and joint pain, among other ailments. In India today the pepper mixture trikatu is relied on to treat a wide variety of illnesses, in combination with other herbal preparations. The mixture contains black pepper, long pepper, and ginger in equal proportions, and is part of most prescriptions in traditional Ayurvedic medicine. Many are taken as pills or powders and are often consumed with honey to make them more palatable. In South Asia pepper is also widely employed in a broad array of folk remedies, especially as a treatment for diarrhea. Most medicines in the West, too, are derived from plants. Willow

bark was the original source of aspirin, and the latest treatment for malaria, artemisinin, is a compound found in a shrub applied in traditional Chinese medicine.

Among spices, turmeric, a spice in yellow mustard and Indian curry, called *haldi* in Hindi and *jiang huang* in Chinese, has been given the most attention by Western scientists because of its potential as a treatment for Alzheimer's, cancer, and other diseases. But scientists have not neglected black pepper, which shares some of turmeric's properties.

Black pepper contains many compounds, but piperine is the most abundant. First identified in 1820 by a Dutch chemist named Hans Christian Orstedt, piperine is considered an alkaloid. (Long pepper, *Piper longum,* also contains piperine.) Alkaloids are common in nature—some 10 to 20 percent of plants contain this type of chemical, according to Van Nostrand's *Scientific Encyclopedia.* Caffeine, heroin, and nicotine are also alkaloids, however there is no evidence that piperine is addictive. Most alkaloids contain the element nitrogen embedded in rings of carbons. Stronger pepper is packed with more piperine, the reason why pepper grown in Malaysia and Indonesia is more pungent than pepper grown in Brazil.

Piperine's propensity to boost the effectiveness of a particular treatment for cancer is the focus of a research project underway at Fox Chase Cancer Center in Maryland led by urologic surgeon Robert Uzzo and scientist Vladimir Kolenko. They are evaluating whether the compound can make a medicine for treating advanced prostate cancer more effective and easier to tolerate. Piperine inhibits a liver enzyme that is responsible for the degradation of a drug called docetaxel, which combats various kinds of tumors. Docetaxel, itself a natural product derived from the Pacific yew tree, is a medi-

cine approved by the U.S. Food and Drug Administration to treat men with cancers resistant to the hormones that are the usual first line of treatment. However, the drug only increases the survival of patients by two to four months and has the usual side effects associated with chemotherapy, such as vomiting, hair loss, and nausea. Docetaxel has to be administered intravenously three times a week, since the liver will destroy the drug in its pill form. Patients would be much more comfortable if the drug could be administered orally. Could the addition of piperine make this possible? If the pepper compound inhibits the liver enzyme, can it increase the amount of time the anticancer agent remains in the bloodstream? Would tumor cells be exposed to the agent for a longer period of time than is otherwise possible, enhancing the effectiveness of the chemotherapy? The physician researchers want to find the answers to these questions.

Piperine may also enhance the activity of a natural product called curcumin, the active ingredient in the spice turmeric, that is the ongoing subject of clinical studies at MD Anderson Cancer Center in Houston and elsewhere. Like pepper, turmeric is an ancient spice that is widely used in traditional medicine in India, where it is most renowned for its capacity to fight inflammation. It was this property that led Bharat B. Aggarwal, chief of the Cytokine Research Section at MD Anderson and a former scientist at the biotechnology company Genentech, to explore the feasibility of using curcumin as an anticancer agent.

Some investigators believe that piperine has the capacity to quell inflammation, which would make it an appealing compound to incorporate into treatments for a wide variety of diseases. The idea that inflammation is tied to cancer stems from the discovery of a substance called tumor necrosis factor, a powerful protein linked to inflammation that also appears to play an important role in driving the growth of tumors. (Aggarwal and his colleagues at Genentech

purified tumor necrosis factor in the 1980s.) This protein is also produced in people with various autoimmune diseases, such as psoriatic arthritis and inflammatory bowel disease, and medicines designed to neutralize it are taken by millions of people worldwide.

The destructiveness of the protein becomes clearer through its relationship to a molecule called nuclear factor kappa beta (NF Kappa B). Tumor necrosis factor activates this molecule, which has been linked to immune and inflammatory processes, cell growth, and many other biological processes. Normal cells have lower levels of NF Kappa B than tumor cells. The interesting observation here is that curcumin and piperine have each been shown to suppress the activity of NF Kappa B. More than eight hundred compounds are also known to inhibit the molecule, though, so further research is needed to figure out if the specific activity of the spice chemicals will have any meaningful effect in the clinic.

Most intriguing are the possibilities of using piperine to improve the bioavailability of curcumin, and combining the two spice ingredients to generate a more powerful response. In a small laboratory study published in 2009 by researchers at the University of Michigan, each compound by itself and in combination inhibited the renewal, or generation, of certain stem cells in the breast that may be the source of cancer cells. Additionally, they found that the compounds did not harm normal tissue, at least in the laboratory setting. Indeed, piperine has been shown in a series of other laboratory studies to inhibit colon cancer in rats induced by a known carcinogen and to protect against DNA damage in animals with induced lung cancer.

Already the Internet is serving up a large dollop of news about pepper's anticancer properties. "Pepper's hot stuff because it contains pungent piperine, which goes into search-and-destroy mode when breast stem cells are trying to turn cancerous," boasts a Web

site bearing the headshots of "Dr. Oz" and "Dr. Mike." "Pass the Pepper," shouts a headline from the *National Post* in Canada, in an article that includes information about piperine's ability to increase the bioavailability of curcumin and to help with weight control, at least according to research on mice.

For anyone inspired to eat a lot of black pepper based on all of these findings and reports, there doesn't appear to be much risk. In animal studies, rats and mice fed up to one hundred times more black pepper than is normally consumed in the Indian diet did not suffer any ill consequences; their gastrointestinal tracts did just fine. Rather than cause distress, some researchers believe that piperine in very high doses may promote digestion and protect the lining of the stomach and intestine.

While black pepper may be associated with promising areas of medical research, it isn't a panacea. Modern research is usurping the long-held notion that pepper is an excellent preservative. Krishnapura Srinivasan, who has studied the physiological effects of piperine for more than thirty years, says that pepper has "limited application" as a preservative, especially in comparison to other spices such as turmeric and garlic. Pepper also appears to fall short in another potentially exciting application, as an antioxidant that squelches rogue oxygen molecules contributing to cancer, hardening of the arteries, and other diseases. Curcumin is effective, but piperine is not.

However, black pepper may have a less exalted role in natural insect repellents. A study published in 2008 by scientists at the University of Florida and the U.S. Department of Agriculture reported that repellents containing compounds called piperidines, which are closely related to piperine, warded off mosquitoes more than three times longer than DEET, the active ingredient in most insect sprays.

DEET was discovered in 1953, and scientists still do not know how it prevents insects from biting. Volunteers in the 2008 study comparing the two wore arm patches laced with the piperidine compounds and bravely held their arms in a chamber filled with about five hundred mosquitoes. The DEET kept the insects away for an average of almost eighteen days, while some of the piperidines were effective for up to seventy-three days. One of the scientists who led the research says that the new compounds have the advantage of being unsticky and unsmelly (surprising for compounds related to piperine) compared to most of today's insect repellents.

Black pepper is not the only member of the *Piper* family of plants that is being investigated by scientists. The intriguing effects of pepper's close relative, *Piper betle,* the foundation of habit-forming betel chewing in Asia, have not gone unnoticed in the laboratory. Ever since Europeans first set foot in Asia, they have observed that betel seemed to promote good health. One of the many travelers to comment on betel's apparently life-enhancing properties was Tomé Pires, the Portuguese ambassador to China in the sixteenth century, who wrote: "It greatly helps digestion, comforts the brain, strengthens the teeth, so that men here who eat it usually have all their teeth, without any missing, even at eighty years of age. Those who eat it have good health and if they do not eat it one day their breath is unbearable."

Like black pepper (*Piper nigrum*), betel is used in Ayurvedic medicine for constipation, headaches, ringworm, conjunctivitis, and other conditions. We also know that it also produces a sense of well-being and increases alertness. In India today, preparations of betel quid, which may combine sliced areca nut, lime, aniseed, clove, coriander, cardamom, or other ingredients with betel leaves, are still offered on ceremonial occasions, such as marriages and religious

festivals. As in the days when Europeans first traveled to Asia, it is still considered impolite not to offer a guest a chew. India isn't the only country where betel is chewed—millions of people in China, Malaysia, Indonesia, and other countries also partake. The leaf is probably the most widely exploited *Piper* sibling, second only to black pepper itself. In fact, some six hundred million people are estimated to consume betel daily. The controversial association of betel leaf with mouth cancer is mainly due to other ingredients, such as areca nuts and tobacco, which are combined with betel to make quid. While in most parts of Asia the betel leaf is essential for making paan, people in the Chinese city of Xiangtan in Hunan Province like to chew only the husk of fresh areca nut, which they call "binglang," the basis for a 1.18-billion-dollar industry. Blackened gums and stained teeth are the hallmarks of crunching the nut.

The interest in natural products has cast a new light on betel, and the spotlight is shining on betel's antimicrobial properties, which probably explain why the leaf seems to preserve one's teeth, as Tomé Pires observed nearly five hundred years ago. Indeed, a study from the department of oral biology at the University of Malaya in Kuala Lumpur, Malaysia, reported that extracts from *Piper betle* and *Psidium guajava* (guava) suppressed the growth of bacteria that contribute to dental plaque.

Other researchers are evaluating an entirely different property of betel, its capacity to inhibit an enzyme called xanthine oxidase. The enzyme is critical to the production of uric acid in the body. High levels of the acid may lead to gout and kidney stones. The drug allopurinol, which inhibits the enzyme, is a treatment. But the drug has serious side effects, such as kidney failure, allergic reactions, and impaired functioning of the liver. Alternatives are being investigated by a research group in Japan. The characteristics of the chemicals found among the plants in the *Piper* family inspired the group to

screen black pepper and its siblings for activity against xanthine oxidase. Among all the plant extracts tested, betel was the most potent inhibitor of the enzyme. They subsequently identified a chemical in betel called hydroxychavicol, which appeared to be responsible for shutting down the enzyme.

Most important are reports in the scientific literature suggesting that betel may combat the parasite that causes a disease called leishmaniasis, which is transmitted through the bite of a tiny sand fly. As many as two million people in the world are currently infected, and every year another one to two million new cases occur, according to the World Health Organization. Few countries are unaffected. There are two forms of the disease, cutaneous and visceral. The manifestations of the cutaneous form are skin sores that can last for years before healing on their own. The sores can be disfiguring if they occur on the face, and some of these volcano-like eruptions are painful.

The visceral, more severe form of the disease affects the internal organs and can be fatal. More than 90 percent of people infected with visceral leishmaniasis live in India, Bangladesh, Nepal, Sudan, and Brazil, according the U.S. Center for Disease Control and Prevention in Atlanta. Current therapies for the visceral form of the disease aren't very effective and have a variety of side effects. Drug resistance is also increasing. So there is a real need to develop new drugs to fight leishmaniasis, and several laboratories in India report that extracts from betel kill leishmania parasites in a laboratory setting.

Scientists are just beginning to explore betel's potential utility as a medicine. While there is no guarantee that these early observations will eventually be turned into therapies, there is hope that its great potential will bring healing to millions.

Epilogue

The roster of countries that produce pepper today hasn't changed much since Europeans first crossed the Indian Ocean to find the spice. It is, after all, a tropical plant with a penchant for a particular type of soil and climate, and it cannot be easily transplanted, as the Portuguese learned when they tried to cultivate the plant in Brazil during the seventeenth century. It took nearly three hundred years for that particular experiment to work, and it was the Japanese who first introduced large-scale pepper plantations into Brazil in 1933. After World War II, pepper was introduced in Africa, and its production expanded in Southeast Asia, particularly in Vietnam and parts of southern China.

Today Vietnam has emerged as the leading pepper grower, contributing about 30 percent of worldwide production, followed by India, Brazil, China, Indonesia, and Malaysia. Black pepper is an integral part of food consumed everywhere, and some 640 million pounds are harvested each year in the world. The highest quality pepper—Malabar garbled and Tellicherry extra bold—is grown in

India, which exports the most pepper to the United States. Traders bet on the market prices of pepper in India, where the spice is traded on a commodity exchange in Kochi. Pepper still is the world's biggest selling spice, and its profitability depends on the vagaries of weather and soil. Demand fluctuates slightly but generally remains fairly steady year to year.

The biggest problem facing pepper growers today is foot rot disease, caused by a fungus with the scientific name of *Phytophthora*. The fungus has spread throughout the world's pepper-growing regions since it was first detected in Indonesia in the late nineteenth century. The invading fungus quickly wilts the green leaves of pepper vines and strangles the roots of the plant, and it has destroyed many small-scale homestead pepper farms in Kerala in India, along with farms in many other pepper-growing areas. In Vietnam the devastating disease is called *quick wilt* or *quick death*. Efforts to keep crops free of this dreaded disease has led to the extensive use of fungicides. An intensive search is underway for hybrid strains that can resist the fungus and reduce the use of fungicides.

Surveying the wreckage of colonization and subjugation in Latin America, the writer Eduardo Galeano observes that "places privileged by nature have been cursed by history." His words could easily apply to black pepper in Asia. The spice that lured the West to Asia gave birth to the modern age of global trade, with all of its attendant miseries. The brutal and racist men who plied the Indian Ocean in search of pepper or in defense of pepper, from Vasco da Gama in the sixteenth century, to the infamous Jan Pieterszoon Coen and Cornelis Speelman in the seventeenth century, and to John Downes in the nineteenth century, reflected to some extent the prevailing beliefs of their day. But there were men who sailed to Asia who did try

to understand other cultures, who were revolted by violence, and who felt inspired by the sheer natural beauty of the places they visited. Their voices, too, deserve to be heard above the din of conquest and imperialism, slavery and genocide. There was the Cornish traveler Peter Mundy, who described in almost adoring terms a pepper garden in India. There was William Keeling, the English East India Company captain who spent a delirious day being fêted in the clear-flowing waters of Aceh. There was the adventurer William Dampier, who was disgusted by the way in which an English administrator of the Benkoolen pepper settlement treated Malaysians. There was the American seaman Levi Lincoln, who unflinchingly reported how the Americans cheated the pepper-weighing scales in western Sumatra. Even Stamford Raffles, the ever-political, ever-calculating servant of the English East India Company, the model of the Company man, reformed the racist laws in the Benkoolen settlement. There were also Europeans who adopted Asia as their homeland, who went native, like Judith of Malacca, the shipwrecked English maidservant who Peter Mundy mentioned in his journals.

Certainly the history of pepper cannot be detached from the rise in the seventeenth century of two great Western mercantile companies, the Dutch and English East India companies. Their rabid, almost never-ending quest for supremacy in Asia over a period of some two hundred years was ferocious, even though in Europe the English and the Dutch were sometimes allied with each other against the Spanish or the French. Occasionally peace prevailed when politics obliged the English and the Dutch to work together in Asia to dispel a common enemy. Over the course of its existence, the VOC employed hundreds of thousands of men and was a vital engine for the economy of the Netherlands, especially during the golden seventeenth century of Dutch history. The company paid large dividends, making its shareholders rich, but the demands of supporting and

arming such a far-flung, fundamentally corrupt organization finally brought the VOC down. The VOC was millions of guilders in debt when it went bankrupt in 1799.

The English East India Company had to adopt the tactics of its Dutch rival in order to thrive, and in the eighteenth century it became a military and political entity to protect its interests in Asia, especially in India. The Company generally left the spice trade to the Dutch and concentrated its efforts in India and China. Its powers began to wane in the late eighteenth century when the movement toward free and open trade took precedence over monopoly trade. The Company withdrew from trade in the East in 1833, but it remained infamously tied to British imperialism in India. The same held true for the VOC, although the Dutch company was always seen as an arm of government. After the company was disbanded, the Dutch government inherited the VOC's holdings, eventually becoming the overseer of the Dutch East Indies, which it ruled until 1949. Both companies left an indelible and horrific mark on the lands and peoples they conquered.

Black pepper, the spice that was the primary reason the northern Europeans established their trading companies, lives on today as a commodity, a common seasoning, and as a potentially valuable medicine in the West. Its history, though, as Voltaire observed some two hundred years ago, is soaked in blood.