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Food at the Crossroads: Chemistry's Role in Sustainability, Past and Present

Mary Virginia Orna, Editor
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New Rochelle, New York

Gillian Eggleston, Editor
Audubon Sugar Institute, LSU AgCenter
St. Gabriel, Louisiana

Alvin F. Bopp, Editor
Department of Natural Sciences, Southern University at New Orleans
New Orleans, Louisiana

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Alcoholic Beverages as the Universal Medicine before Synthetics

Patrick E. McGovern*

University of Pennsylvania Museum of Archaeology and Anthropology, Philadelphia, Pennsylvania 19104, United States

***E-mail: mcgovern@upenn.edu.**

Fermentation (anaerobic glycolysis) was probably the first energy system on Earth. It is embodied in the metabolic cellular structures of aerobic organisms, including ourselves, as the Krebs (tricarboxylic acid/citric acid) cycle. Our ancestors applied fermentation to produce alcoholic beverages from high-sugar natural products (e.g., fruits, honey, tree saps, and saccharified roots and grasses), which were available in temperate climates worldwide. The alcohol in the drinks served as a combination antiseptic, analgesic, and anesthetic and was much safer than untreated water. Alcohol was also more effective than water in putting botanical compounds with medicinal properties—derived mainly from herbs, spices, and tree resins—into solution, which could then be administered orally or topically through the skin. As such, alcoholic beverages were incorporated into pharmacopeias around the world, both written (e.g., Egypt, India, China, Greece, and Rome) and unwritten, before the advent of synthetic medicines over the last century and a half. As biomolecular archaeological techniques become increasingly more sensitive and precise, they open up the prospect of "re-discovering" effective, innovative remedies of our ancestors. This phenomenon is illustrated by our research on ancient Chinese fermented beverages.

With our ever-accumulating knowledge of human biology, physiology, and genetics during recent decades, we are apt to think that humans have long had ready at hand an arsenal of chemical compounds, many synthetically produced from highly processed starting materials. Indeed, it might be claimed that we can now construct de novo our own compounds from an infinite range of possibilities and target specific diseases and other medical conditions, so why restrict ourselves to only naturally occurring ones found in nature?

An exclusively de novo approach, however, fails to recognize that the starting materials used to make synthetic medicines are themselves very frequently derived from natural products. Moreover, herbal and other botanical remedies, which are sometimes described as alternative, complementary, or integrative, continue to play major roles in modern medicine. Aspirin, for example, is derived

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from willow tree bark (*Salix* spp.), and it remains the most widely used pharmaceutical palliative used today. Ancient Mesopotamian, Egyptian, and Greek texts pointed the way to the isolation and eventual modification of salicylic acid in the 19th century (*1*). Quinine, which comes from the bark of South American trees and shrubs (*Cinchona* spp.), is one of the best treatment options for malaria. It has been recognized as effective against malarial fever by native Peruvians since at least the 17th century. A compound found in yew needles and bark (*Taxus canadensis*), paclitaxel, is the drug of choice in treating ovarian and breast cancers, and is now the largest selling anticancer medicine (TAXOL) in the world (*2*). North American native peoples were seen making a tea from it to treat arthritis, rheumatism, and other ailments by early European explorers (*3*).

Many other examples of taking a traditional natural remedy, as based on ancient written pharmacopeias, ethnohistorical texts, and ethnographic observations, and effectively incorporating it into modern medicine might be cited ((*4*, *5*), compare (*6*)). I can personally attest to the beneficial medicinal effect of at least one South American plant. While preparing a book on ancient Egyptian pottery in Austria, I was laid low by an excruciating toothache. The University of Vienna's dental institute was unable to provide relief with synthetic medicines after a week of suffering, so I turned to a private dentist. He prescribed a Peruvian tree sap of uncertain species, which had me up and smiling within an hour.

Clearly, plant exudates and structures of all kinds (e.g., resins, nectar, flowers, roots, leaves) have figured importantly in drug discovery. Yet, of the nearly 400,000 plant species currently known and growing, with new discoveries every year, at most about 70,000 (17.5%) have been screened for their medical effectiveness (*7*) and even fewer, on the order of 5,000 (1.5–2%) (*8*), had been exhaustively studied as of 2007 (*9*). Plants have generally been chosen for analysis based on traditional medicine (*10*). This approach makes good sense, because constructing and testing an exhaustive library of de novo synthetic compounds would be daunting. Nature has already carried out combinatorial chemistry on a vast scale to produce compounds, particularly secondary metabolites, that serve to ward off disease and noxious organisms, to prevent premature death (e.g., by cancer), and to promote growth and other physiological functions.

When the abundant productivity of nature is coupled with human observation and experimentation by trial and error over hundreds of thousands if not millions of years, stretching back into the Paleolithic period, then the prospects for drug discovery become even greater. Our human and hominin ancestors had a large incentive for exploring the world around them for possible remedies against diseases and physical ailments. Lacking modern synthetic medicines and suffering from numerous maladies that resulted in infant death and short life spans, their only recourse was to "experiment" with plants, other animals, minerals, and microorganisms. Although the latter are microscopic, their effects might be visually apparent, as when the fermentation of sugary concoctions is accompanied by the evolution of carbon dioxide. Their experimentation was not the rigorous scientific testing that we demand today, but if a remedy had no observable practical effect, we might expect such a false-positive eventually to be culled out over time. On the other hand, superstitions, misguided religious injunctions, or unfounded psychological notions might creep into a tradition (e.g., submerging a rhinoceros horn or bull's penis in a modern Chinese wine to convey its strength or other sympathetic attribute).

Efficacious medicines might well have been discovered during innovative periods when traditional approaches were open to new ideas, such as the Neolithic Revolution in which numerous plants were domesticated in "centers of origin" around the world, including east Asia, the Near East, the Andes and Amazonia in South America, southern Mexico, the African Sahel, and New Guinea

(*11*). Depending on the vagaries of human oral and written traditions, as well as cultural collapse and destruction by natural and manmade calamities, any "discovery" might subsequently be lost.

Biomolecular archaeology now enables us to discover medicinal effects of herbs, tree resins, and so forth going back even earlier than written evidence and without testing every plant in the jungle. Ancient humans and modern practitioners have already done this for us. The medicines of ancient societies, which have been destroyed and are now gone, can be brought back to life. Our project pursuing this objective, done in collaboration with the University of Pennsylvania's Abramson Cancer Center, is aptly called "Archaeological Oncology: Digging for Drug Discovery (D^3)" (*12*).

Setting the Stage for Archaeological Pharmaceutics

To understand why ancient alcoholic beverages in particular might be a key to drug discovery in the present, we need to turn back the clock to the beginning of life on Earth some 4.5 billion years ago. A plausible theory for how life began is that single cells (prokaryotes) self-organized metabolic and replicative chemical pathways that enabled them to produce energy from simple sugars by an anaerobic fermentation process (glycolysis) (*13*), with alcohol and carbon dioxide as the possible end products. A modified aerobic fermentation process—variously known as the citric acid, Krebs, or tricarboxylic acid cycle—still powers every living organism on Earth, including the approximately 40 trillion cells in our bodies. Although life is vastly more complex today, the essential process of energy production can then be envisioned as having been quite similar since the beginning.

Fast forward to the Cretaceous Period of 145–65 million years ago when most of the life forms we see around us today emerged. The first flowering fruit trees and shrubs appeared then, which our ancestors later exploited for making alcoholic beverages. They provided food resources (fruit, nectars, and saps) for the animals, who in turn pollinated them. Honey bees came on the scene, taking these sweet essences and making the most concentrated source of sugar in nature: honey. Among many other insects that feed on both sugar and alcohol, fruit flies made their appearance. Like ourselves and most other animals, they sometimes overindulge and get drunk. They have been shown to have the same genes for inebriation as humans have, which are given such fanciful names as *amnesiac*, *barfly*, *cheapdate*, and *happyhour* (*14*). Other higher animals share the same genes.

Dinosaurs were also integrated into the emergent ecological system, as attested by birds, which are descended from them. For example, when zebra finches overindulge in fermented fruit, their songs become confused and more subdued due to alcohol's effect on their syrinx and brain (*15*). Likewise, when we get drunk, our homologous larynxes and brains can produce slurred and muffled speech.

A genetic modification of the wine-beer-and-bread (baker's) yeast (*Saccharomyces cerevisiae*) (*16*, *17*) is especially important because it serves as the worldwide workhorse fungus in making the alcohol in all fermented beverages. During the Cretaceous period, its genome was duplicated (*18*), resulting in two versions of the alcohol dehydrogenase (Adh) gene, which produces two versions of the enzyme (ADH). One version of the enzyme (ADH1) converts acetaldehyde, the end product of glycolysis, into alcohol in an oxygen-free environment. The yeast literally swamps its enemy microorganisms in alcohol; because most microbes cannot tolerate alcohol levels above 5%, they die. The yeast cell can tolerate concentrations of 12–15%, sometimes more than 20%. Once the competition has been eliminated and oxygen levels start to rise again, the other form of yeast's enzyme (ADH2) goes into action. It converts alcohol back into acetaldehyde and ultimately generates much more ATP (adenosine triphosphate) through the Krebs (tricarboxylic acid/citric acid) cycle

that requires oxygen. The delayed gratification has been worth the wait, now that the competing microbes, often harmful to other living organisms, have been destroyed. The trade-off is that the yeast produces less ATP, the energy compound of the cell that enables synthesis of the essential organic compounds for life, than would otherwise be possible.

Yeasts and other microorganisms took the newly available sugar resources of fruit and honey and fermented them into alcoholic, aromatic concoctions that attract animals, who sense the pungent aromas and happily consume them for energy and presumably enjoyment.

Over the course of the Cretaceous Period, new fruiting trees, new insects, new dinosaurs, and new yeasts emerged and were bound together into an intricate web of ecological symbiosis and mutualism. A new level of complexity was added when the supercontinent of Pangaea began to break up into the seven continents that we are familiar with today. Over millennia, land masses drifted apart, separating populations of flora, fauna, and microorganisms from one another and leading to new organisms and integrated communities (*19*).

Despite geographical and temporal variations, the long-term availability of the alcohol molecule itself assured it a central, continuing role in the genetic and physiological processes of biological communities worldwide, some of which remained largely the same since Cretaceous times.

A Primate Love for Alcohol

Following time's arrow from the past up to the present, our own order of primates came on the scene about 55 million years ago, as putatively first represented by the pen-tailed Malaysian treeshrew (*Ptilocercus lowii*) (*20*). Curiously and foreshadowing our own propensity for alcohol consumption, these creatures binge on fermented bertam palm nectar all night long, drinking the equivalent of nine glasses of 12% alcoholic wine for the average human (*21*). In contrast to humans, who would be certifiably drunk at this stage, the treeshrew shows no signs of inebriation.

Modern primates in turn generally have diets composed of about 75% fruit in keeping with their dentition (small molars and canines), which is best-suited for soft foods, and they are known to eat as much fermented fruit or drink as possible when available. Robert Dudley, in his book *The Drunken Monkey* (*22*), demonstrates this for howler monkeys in Panama, which consume a fermented palm fruit, putting away the equivalent of about two bottles of grape wine in 20 minutes. Kimberley Hockings and colleagues (*23*) report how wild chimpanzees, who are closest to us genetically (96% correspondence), improvise leaf "sponges" in West African Guinea to facilitate lapping up about one bottle of a 3–6% alcoholic palm wine daily. West African chimpanzees have also been observed improvising tools, including sharp-ended sticks and long, flexible vines, to extract honey from beehives (*24*), presumably in advance of human efforts in this direction to make a fermented beverage.

Our hominin and human ancestors in Africa were likely genetically and physiologically endowed to consume and enjoy an alcoholic beverage, as we and other primates are today. Soft tissues and other organic evidence for the Paleolithic period, going back some 4 million years and representing 99% of human existence, may be very thin on the ground. But fossil skeletons, not so dissimilar to our own, imply that our forerunners had the necessary sensory apparatus—the color vision to be attracted to brightly colored, readily fermentable fruit; olfactory bulbs to detect alcohol and associated aromatics; and taste buds to appreciate a myriad of flavors produced by glycolysis and subsequent reactions. Brain endocasts bear out these conclusions (*25*), besides implying that the requisite structures and presumably the neurotransmitters (dopamine, serotonin, opioids, and other

compounds) for cellular intercommunication were already present for unleashing a "pleasure cascade" and mind-altering experience when alcohol was consumed (*26*).

The relatively small teeth of Paleolithic hominins again point to a diet of soft foods, which has been bolstered by isotopic and phytolith studies of natural products embedded in plaque, principally fruits and wild grasses of the C-3 metabolic pathway (*27*).

Moreover, like yeast, a suite of alcohol dehydrogenase enzymes was available to hominins for converting alcohol into energy. A comparative study of variants of the ADH4 enzyme (*28*), present in the mouths, throats, and stomachs of many primates as well as humans, indicates that it came into existence about 10 million years ago when the human and ape lineages separated and humans began to exploit wild grasses and other resources of the African savanna in addition to forest fruits. This enzyme would have increased our ancestors' ability to digest alcoholic foods and beverages, which is mainly carried out by ADH1 and ADH2 in the liver. Human livers, the real powerhouses for churning out energy from both sugar and alcohol, are composed of about 10% of these metabolic enzymes.

Fermentation by countless bacteria, fungi, and other microorganisms of foodstuffs outside the body, during a "predigestive" phase, was likely also important to prehistoric humans. Such food processing would have been followed up by the communities of beneficial and symbiotic microorganisms inhabiting their and our gastrointestinal tracts.

The First Biotechnology

In short, the modern human is preprogrammed to detect, process, and enjoy an alcoholic beverage. From the moment we take a sip of our drink of choice and alcohol crosses the blood–brain barrier—and even before when we consider the possibilities of what the natural product has in store for us—genes and enzymes go into action. It doesn't take a great leap of imagination then to posit that early hominins, our ancestors, some 200,000–100,000 years ago in Africa, were already acting in the role of *Homo imbibens*, making wines, beers, and mixed or extreme beverages with many ingredients, from wild fruits (maybe figs, dates, or baobab fruit), honey, chewed grains and roots, and all manner of herbs and spices culled from their environments. The only caveat is that, because of the limited possibilities for drinking an alcoholic beverage in Paleolithic times, our bodies and brains are adapted to moderate consumption. When we overindulge in alcohol (thus violating the general biological principle of hormesis in which moderate consumption of a substance that might be dangerous when taken to excess can be positively good for you), we pay the medical consequences.

Besides fruit juice, tree sap, and flower nectar, which readily ferment to wine because of resident yeast, honey, as the most concentrated source of sugar in nature, can easily be fermented to mead when diluted with water at a ratio of about 30% to 70%. Native hyperosmotic yeasts then become active and ferment the honey to mead.

Roger Morse, who wrote the pioneering book on the subject (*29*), proposed that mead making was the first biotechnology of humans. He theorized that a honey hunter, a well-respected "occupation" in Mesolithic and Neolithic times (as shown in African and European rock art), was making his or her rounds and discovered that a beehive in a hollow of a dead tree on the ground had been filled with the requisite amount of rainwater and had been converted into mead. One smell of the new aromas emanating from the hive and one taste of the mind-stunning liquid were all it took to get the idea that perhaps the fermented beverage could be made with a little help from humans (most likely women, who were generally the fermented-beverage makers of antiquity). A container would be needed and that might be improvised from wood, an animal skin, or woven grass. Unfortunately, no containers have yet been recovered from Stone Age sites, so definitive analytical support for this hypothesis is thus far lacking.

Hominin production of a fermented beverage from a carbohydrate resource, such as a wild grain, tuber, or plant leaves and stems, also cannot be ruled out. The enzyme ptyalin in our and likely in our ancestors' saliva belongs to the amylase/diastase class, which are active in the saccharification (malting) process of beer making in which starches are cleaved into sugars to be fermented. Given the natural impulses to suck and chew, our ancestors might well have masticated plant products and observed that their sweetness was intensified. If they then expectorated (spit out) the liquid, the latter might have been inoculated with yeast by an insect feeding on the sugar, thus producing a fermented beverage.

Corn chicha has long been made by the chewing-and-spitting method throughout the Americas and was incorporated into the social and religious traditions of the principal cultures, including Inca, Maya, and Aztec (*30*). A strong archaeological, genetic, and isotopic case (*31*) can be made that chewing the wild grass teosinte in Archaic (Upper Paleolithic) caves of west-central Mexico, as attested by masticated cakes (quids), contributed to human fascination with the plant, ultimately leading to its domestication as maize (corn). The primary goal of all this chewing, in addition to the creation of a highly concentrated and nutritious sugar resource (note that one kernel of maize is equivalent to that of an entire teosinte plant and there are 500 or more kernels in a single corn ear), was to make an alcoholic beverage.

The goal of making a fermented beverage, probably originally by the chewing-and-spitting method, appears to have led to the domestication of other major cereals worldwide, including barley, wheat, rice, sorghum, and millet (*32*, *33*). Modern examples, probably with long precedence, include women in the eastern Sahel of Africa making a sorghum beer this way, and in Japan and Taiwan, groups of women chewing rice to prepare an alcoholic beverage for marriage ceremonies.

These were no ordinary drinks, but they had significant social and biological ramifications. Besides the sheer psychoactive delight in their new-found beverages, fermentation produced more nutritious, sensorially appealing, and preservable foods than the starting materials. They served to bring people together as a group in their roles as "social lubricants" by breaking down inhibitions between them. We can still see this going on around us today in taverns, homes, and celebrations of every kind. An alcoholic beverage was additionally a combination relaxant or anesthetic (perhaps after a hard day of hunting and gathering), sleep inducer, and aphrodisiac.

The mind-altering effects of a fermented beverage, as well as the mysterious process of fermentation itself, in which a liquid is radically transformed with the violent evolution of a gas (N.B., yeasts were seen microscopically for the first time in the 17th century and their biological function was elucidated by Louis Pasteur only a century and a half ago), probably account for why fermented beverages were so readily incorporated into religions around the world. While rice and millet beers took hold in east Asia, becoming central to religions there, grape wine emerged as the most significant fermented beverage in the Middle East and western countries. In Africa, where our species began, modern cultures, which perpetuate more ancient traditions that can be broadly characterized as shamanistic, are awash in sorghum and millet beers, honey mead, and banana and palm wines. Each community generally has its own preferred alcoholic drink. Often, the production facility is placed at the center of the village, because of the many activities that revolve around the drink. These alcoholic beverages, especially made from cereals, have been estimated to provide more than half of the energy needs of the African population of more than a billion people.

Alcoholic beverages additionally might well have opened the human mind to new possibilities of thought. Among many creative activities, perhaps some grunts might have been varied to produce a kind of music or communication, which eventually led to true language, syncopated body movements might have resulted in dance, and visual representations might have led on to cave art. Some modern thinkers, musicians, and artists carry on in such primitivist traditions.

Finally, and of great significance, alcoholic beverages became the universal medicine of humankind for thousands, perhaps millions of years, before the advent of synthetic drugs in the 19th century (*34*). This phenomenon was partly due to the worldwide availability of fermentable substrates. After our ancestors came "out of Africa" about 100,000 years ago, they were confronted with a host of new plants, which they explored for their medicinal properties by applying traditional methods and improvising, if necessary.

Alcohol was crucial to our ancestors' palliative and curative endeavors. During prehistoric times when synthetic drugs were unavailable and one's life span, if one survived birth and childhood, was 20–30 years, a fermented beverage's health benefits were obvious—alcohol relieved pain, stopped infection, and seemingly cured disease. Today, we know that its moderate consumption lowers cholesterol and prevents some cancers. Those who drank fermented beverages, rather than water, which could be tainted with harmful microorganisms and other parasites, lived longer and consequently reproduced more. Herbal or tree resin compounds with medicinal properties could also be more easily dissolved in the alcoholic medium and readily applied to the skin or by drinking (*35*). "Medicinal wines" and external salves, with analgesic, anesthetic, antimicrobial, and psychotropic properties, are recorded in later pharmacopeias from around the world. By using biomolecular archaeological techniques, humankind's first medical forays can be pushed back into prehistoric times.

Ancient China: A Paradigmatic Example of Alcoholic Beverages Being the Universal Medicine of Humankind

I would argue that no single fermented beverage took precedence over any other in being discovered first, whether a wine, mead, beer, or a more complex concoction—an extreme beverage—with numerous ingredients. All the biological pieces of the puzzle for intentionally making an alcoholic beverage were there—the natural products, the inquisitive hominin and human brain, the sensory awareness, and so forth—and in place from the "beginning" of our species, as it were. Our omnivorous diet is testimony to our openness to trying out new foods and mixing them together.

We may never know how, when, and where the initial discovery of an alcoholic beverage took place during the Paleolithic period, but as new archaeological excavations are carried out and scientific instrumentation continues to improve, we will undoubtedly learn more. We can imagine but not yet prove that an enterprising "first fermented-beverage maker" likely threw some ripe fruit, diluted honey, or masticated wild grain into a primitive container made of wood, woven grass, or an animal skin, and voilà, you had your drink! Lacking a glass bottle and cork of much later times, however, you had to consume it quickly before it turned to vinegar! You could call it a Stone-Age Beaujolais Nouveau or a sour ale or mead. The drink might have been passed around to the assembled group for their opinions, later to become a staple or traditional drink.

But we now have a starting point (a terminus ante quem in archaeological parlance) from which to look back on the great expanse of early hominin and human existence. The early Neolithic site of Jiahu (*36*) in the Yellow River valley of China currently holds this distinction. According to chemical and radiocarbon analyses, the village people there were making, drinking, celebrating with, and enjoying an extreme fermented beverage of wild grapes, hawthorn tree fruit, honey, and rice around 7,000–6,000 B.C.E.

You might have thought, as I first did as a Middle Eastern archaeologist, that the Fertile Crescent of the Near East, the so-called "Cradle of Civilization," would have come first, and that may still be the case as we continue analysis of stone vats from Göbekli Tepe in eastern Turkey (*37*). China had

at least one point in its favor: Pottery was being made there as early as 16,000 B.C.E., some 10,000 years in advance of the Near East.

Once pottery enters the picture, the prospects for preserving and identifying ancient organics markedly changes. Porous earthenware pottery, made from aluminosilicate clays, is able to absorb ancient organic compounds, especially in liquid form, and hold them relatively intact for centuries, even millennia.

We focused our efforts at Jiahu on jars with high necks and flaring rims, which were ideally shaped to hold and serve liquids (Figure 1). The question was: What was the beverage inside the vessels? We used a battery of chemical tests, including infrared spectrometry, gas chromatography-mass spectrometry (GC-MS), isotope analysis, and purge-and-trap thermal desorption (TD) GC-MS, to ferret out the fingerprint compounds or biomarkers of the natural product ingredients of the original beverage.

Figure 1. Early Neolithic jars, with high flaring necks and rims, from Jiahu (Henan province, China), ca. 6,000–5,500 B.C.E. Analyses by the author and his colleagues showed that such jars contained a mixed fermented beverage of rice, honey, and fruit (hawthorn fruit and/or grape). (Photograph courtesy of J. Zhang, University of Science and Technology in China, and Henan Institute of Cultural Relics and Archaeology, nos. M252:1, M482:1, and M253:1 [left to right], height 20 cm [leftmost jar].)

As we analyzed the extracts from one pottery vessel after another, the same chemical compounds kept showing up (*38*). There were beeswax compounds, which we had previously detected in our analyses of the Midas extreme fermented beverage (*39*), showing that one of the constituents was high-sugar honey. These compounds reliably marked the presence of honey in the residues, because it was impossible in antiquity to completely filter them out during the processing of honey. We also found tartaric acid, the biomarker of grape and wine in the Middle East. In China, however, it could also mark the presence of hawthorn tree fruit (*Crataegus pinnatifida* and *cuneata*), which contains three times the amount of the acid in grapes. We don't know yet whether only a wild Chinese grape species or hawthorn fruit, or both, went into the beverage. After we published our chemical results, an archaeobotanical study showed that only those two fruits were present at the site. While

nicely corroborating our findings, we were still left uncertain. Finally, close chemical matches with phytosterol ferulate esters pointed to rice as the third main ingredient, which was archaeobotanically attested by grains intermediate in form between wild and domesticated. Yeasts associated with the high-sugar fruits and honey would have assured the liquid's fermentation.

You could call this extreme fermented beverage a "Neolithic grog or cocktail." It combined honey mead, a rice beer, and a grape and/or hawthorn tree fruit wine. As such, it was the earliest wine, beer, and mead, albeit in combined form, in the world. Such a hybrid fermented beverage might sound strange and unappetizing, as had the Midas extreme fermented beverage when we first chemically identified it. As we've learned over the past 15 years, however, mixed fermented drinks were generally the rule in antiquity, especially during Neolithic times when plants were first domesticated and fermented beverages began to be produced in quantity. By combining multiple sugar sources, our ancestors appear to have accidentally hit upon a solution to a never-ending quest: upping the alcohol content as much as possible.

Distillation technology, although a relative latecomer in China and the Middle East around the turn of the millennia from B.C.E. to C.E., was another human invention that had profound consequences for increasing the alcohol content of naturally fermented beverages. Complex formulations of bitters, digestives, and cure-alls eventually found their way into the pharmacopeias of both the East and the West.

The Jiahu beverage was improvised during a revolutionary era when many plants and animals were first domesticated, thus laying the foundation for year-round habitation and civilization as we know it. Jiahu led the way in this lifestyle with the earliest playable musical instruments (bone flutes), silk textiles, domesticated rice and pig, fish breeding, putative pictographic writing on tortoise shells for divination, and, of course, a suitably complex and delicious alcoholic beverage to sustain one both in this life and the next.

China is all about long traditions, and today people in China still communicate with their ancestors via a high-alcohol rice or millet beer. A family intermediary consumes nine large goblets, some 4.5 liters of a 10–12% alcoholic drink, enough to assure inebriation. This is only fitting, since "the spirits are all drunk" (*40*) and drunkenness is the only way to communicate with them. Bells are rung and drums beaten at the ceremony's conclusion. We can imagine 9000 years earlier, the Neolithic flutes in the Jiahu tombs having served a similar purpose. The jars with the "Neolithic cocktail" were carefully placed near the mouths of the deceased, perhaps for easier drinking in the afterlife. The practice of communicating with the dead by a fermented beverage goes back at least to the Shang Dynasty (ca. 1600–1046 B.C.E.), based on written evidence.

Getting drunk to communicate with the dead was one use for an extreme fermented beverage. Another advantage of such a drink was its health-giving properties, including alcohol itself and any botanicals with medicinal value dissolved into it. Since we have not yet analyzed the extracted residues from the Jiahu jars by solid-phase microextraction (SPME), TD GC-MS, or a comparable technique capable of detecting low-molecular-weight aromatic compounds, it is not known whether any herbs or spices, which might have anticancer or other medicinal properties, were added to the ancient mixed beverage. The primary natural ingredients in the Jiahu extreme fermented beverage, especially honey (*41*), hawthorn fruit (*42*), and grapes (*43*), however, do have positive health benefits and are still used in Traditional Chinese Medicine (TCM).

The Jiahu finding is obviously very important for the history of Chinese medicine, which was already being written down in the earliest texts—the oracle bone inscriptions of the late Shang Dynasty (ca. 1200–1046 B.C.E.)—and then continued to develop over the next three millennia to become TCM. In recent decades, the latter has been put on a much more solid scientific basis (e.g., (*44*, *45*)).

By Shang Dynasty times, however, herbs were clearly part of an already highly specialized medicinal wine "industry." One wine (*chang*) was specifically denoted as herbal in the oracle bone inscriptions. Officials in the Shang palace administration were charged with making the beverages, which the king inspected.

The literary evidence was borne out by our TD GC-MS analysis of an ancient liquid, amazingly still contained inside a lidded bronze jar (Figure 2). The sample came from an upper-class tomb, not far from Jiahu in Henan Province, that dated to the later Shang Dynasty and early Western Zhou dynasties (ca. 1250–1000 B.C.E.), contemporaneous with the oracle bone inscriptions. It yielded, as so many other tombs of the period have, numerous bronze vessels, more than 90 in this instance. When they were shaken, 52 were found to still contain a liquid from 3000 years ago. Because of the tight lids on the vessels, which had corroded to the neck, the liquid inside had only partly evaporated—generally down to about a third or less of its full capacity—and then had been hermetically sealed off until it was excavated thousands of years later.

Figure 2. Bronze you jar, which contained a medicinal rice beer that was still liquid when it was recovered in 1998 from the Changzikou tomb, dated ca. 1250–1000 B.C.E., in Luyi Country, eastern Henan Province. (Photograph courtesy of J. Zhang and Institute of Cultural Relics and Archaeology of Henan Province.)

Equally amazing, the liquid had the characteristic fragrance of a fine rice or millet beer made the traditional way, slightly oxidized like sherry but also perfumy and aromatic like an aged lambic beer, a complex sour brew made with wild yeast and numerous other microorganisms native to the Senne River Valley, near Brussels.

Our TD GC-MS analysis (Figure 3), as part of our "Digging for Drug Discovery" (D^3) project, revealed that two aromatic compounds—camphor and α-cedrene—were present in the ancient beverage, in addition to benzaldehyde, acetic acid, and other short-chain alcohols that are characteristic of rice and grape wines (*46*). Stable ^{13}C and ^{15}N isotope measurements identified the beverage as made from a plant using the C-3 metabolic pathway, most likely rice.

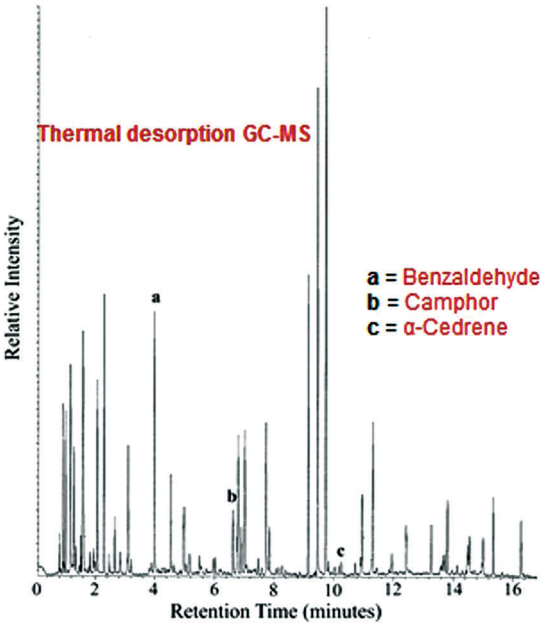

Figure 3. Thermal desorption GC-MS analysis of lidded you jar from the Changzikou tomb. Chromatographic peaks a, b, and c are due to benzaldehyde, camphor, and α-cedrene, respectively. Possible wine-derived propanoic acid derivatives account for the two most intense peaks near 10 minutes. Other peaks correlate with ubiquitous environmental contaminants, especially phthalates.

Based on a thorough search of the chemical literature, camphor and α-cedrene might have originated from a specific tree resin (China fir = *Cunninghamia lanceolata* [Lamb.] Hook.); a flower of the chrysanthemum family; or an aromatic herb, specifically *Artemesia annua* or *A. argyi* in the wormwood/mugwort genus (N.B., Shin (*47*) now reports α-cedrene to be present in *A. annua*; also see (*48*)). If an *Artemesia* species explains the presence of camphor and α-cedrene, then the plant's leaves had probably been steeped in the rice wine, as is still done in TCM. An open vat found in the Changzikou tomb, which was filled with aromatic *Osmanthus fragrans* (tea olive) leaves and held a ladle, pointed to this method of preparation of the ancient beverage, which is still popular today for making flavored or medicinal tisanes and drinks.

Of the possible ingredients and additives identified in the Changzikou rice beer, the two species of *Artemisia* stood out because of their long-standing importance in TCM up to the present day. *A. annua* (designated as belonging to the wormwood family) and *A. argyi* (in the mugwort family) are equated in TCM with qinghao and ai ye, respectively (*49*). These herbs were cited in the earliest

Chinese medical prescriptions written on bamboo and silk strips, found in the extraordinary tomb of a noblewoman at Mawangdui in Hunan province, dating to 168 B.C.E. (*50*, *51*). The woman is said to be the most well-preserved human corpse ever discovered, with the tissues of her internal organs still intact and moist. In the texts, qinghao is prescribed for female hemorrhoids and as a sexual tonic, being mixed with other herbs, including cinnamon and ginger, and administered in boiled urine. Ai ye was also administered in a grass broth as a sexual stimulant and was burned with willow fungus to treat hemorrhoids. It later was used in the very important practice of moxibustion, in which *A. argyi* leaves were burned, often on the tips of acupuncture needles, and applied to the key points on the body.

The monumental "Compendium of Materia Medica" (*52*) by Li Shizen, published in 1596 C.E., attests to the long medicinal use of *Artemisia* herbs in TCM when it cites Ge Hong's (284–364 C.E.) "Handbook of Prescriptions for Emergency Treatment." As for the highly developed ancient Egyptian pharmacopeia (*53*), it is likely that ancient Chinese physicians had detailed anatomical knowledge of the human body, including many different cancers, and would have developed remedies targeted at those cancers.

Artemisinin, a sesquiterpene lactone derived from *A. annua*, proved to be the most important active compound found in our extensive literature search of the species and as confirmed by our in vitro cell line tests against colon and lung cancers (*54*). For her pioneering work in elucidating the structure of artemisinin, the Chinese chemist Youyou Tu was awarded the Nobel Prize in Chemistry in 2015.

Artemisinin's semisynthetic analogue, artesunate, proved more effective than wholly synthetic compounds against colon cancer and many other cancers, including Kaposi's sarcoma, uveal melanoma, hepatoma and ascitic liver tumor, ovarian cancer, pancreatic cancer, neuroblastoma, and myeloid leukemia (see references (*29*–*38*) in (*54*)). Artesunate is also more readily absorbed by the body than artemisinin and has lower toxicity. Both compounds have other medicinal effects against malaria, bacterial and viral infections, and hepatitis B and C (*55*).

Because of the importance of *A. annua* in TCM, it was chosen during the Vietnam War as a prospective herb for testing against malaria (*56*). The anticancer properties of the herb's principal active compound, artemisinin, were subsequently discovered and still remain to be fully elucidated (see, e.g., references (*41*–*54*) in (*54*)). Efferth and colleagues (*57*) have proposed that artemisinin's anticancer mechanism of action is via the endoperoxide linkage of the compound. The latter opens up and creates free radicals that oxidatively react with intracellular components, leading to apoptosis of cancer cells. Intracellular ferrous iron has been implicated in this reaction. Artemisinin/artesunate is now the medication of last resort for malaria.

Another active compound that showed promise against cancers in our *in vitro* screening—isoscopoletin, a coumarin flavone—has thus far been obtained from only *A. argyi* in this genus. Other researchers (*58*) have documented this compound's cytotoxicity against leukemia cells, likely by inhibiting the activity of farnesyl protein transferase. Both *A. argyi* and *annua* are sources of borneol, a monoterpene, which also exhibited some anticancer activity in our study.

It is possible that the use of these wormwood/mugwort plants in fermented beverages, in addition to many other botanicals that make up the ancient and modern materia medica of TCM, goes back much earlier, perhaps even to Neolithic times at Jiahu. Further study is needed, especially by employing ever-improving archaeological, archaeobotanical, chemical, and other scientific techniques and strategies.

Conclusions

Ancient China provides excellent examples with significant findings to date of how alcoholic beverages became the basis of human medicine after our ancestors "came out of Africa" about 100,000 years ago. Whether by applying prior traditions that they brought with them in their travels or by the innovative experimentation of our species, humans successfully took newly found natural products of a region, variously discovering their sensory and medicinal properties, and converted them into nutritious, healthful, and socially significant fermented beverages, often of the extreme type.

As one follows human peregrinations around the world, many other alcoholic beverages made from every kind of ingredient can be documented archaeologically and scientifically. Our ancestors' discoveries were incorporated into the many pharmacopeias of advanced cultures with written languages globally. In those traditions, alcoholic beverages, often with dissolved botanicals, are overwhelmingly the principal means to treat ailments of all kinds.

Our studies of the fermented beverages of Egypt, Turkey, Italy, Scandinavia, Mesoamerica, and Peru are just the beginning. Much more remains to be discovered. These beverages are indeed the universal elixir of humankind, which sustained us in the past and continues to do so in the present.

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Biographical Information

Patrick E. McGovern is the scientific director of the Biomolecular Archaeology Project for Cuisine, Fermented Beverages, and Health at the University of Pennsylvania Museum in Philadelphia, where he is also an adjunct professor of anthropology. Over the past two decades, he has pioneered the interdisciplinary field of Biomolecular Archaeology. His laboratory discovered the earliest chemically attested alcoholic beverage in the world (ca. 7000 B.C., from China), as well as the earliest grape wine, barley beer, mead, and fermented chocolate beverages. He has published three books on ancient alcoholic beverages: Ancient Wine: The Search for the Origins of Viniculture (Princeton University, 2003/2006), Uncorking the Past: The Quest for Wine, Beer, and Other Alcoholic Beverages (Berkeley: University of California, 2009/2010); and Ancient Brews Rediscovered and Re-Created (New York: WW Norton, 2017), together with numerous articles (see http://www.penn.museum/sites/biomoleculararchaeology/).

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